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Symposium on Phonocardiography

Introduction

THE COMPLEX vibratory phenomenon of the chest wall caused by the action of the heart represents the superimposition of pure sinusoidal waves of different amplitudes and frequencies, which extend from the *basic frequency* of the heart beat (0.5 to 2 cycles per second for rates between 30 and 120/min) to over 1,500 cps. Following a law of physics which states that the amplitude of such vibrations decreases according to the inverse square of their frequency, the low-frequency vibrations will be thousands of times larger than the high-frequency vibrations, a fact which creates a complex technical problem of recording.

The entire spectrum of vibrations can be divided into the following five ranges:

Ultra-low-frequency vibrations (studied by Dressler, Luisada, Rosa, Johnston, Eddleman, and others) = 0–5 cps (palpatory or infrasonic range).

Low-frequency vibrations (studied by Rosa, Mounsey, and others), 5–25 cps (lower subliminal or borderline range).

Medium-low-frequency vibrations (low auditory range), 25–200 cps (studied by Rappaport and Sprague, Luisada, and others).

Medium-high-frequency vibrations (auditory), 200–500 cps (studied by Mannheimer, Leatham, Holldack, and others).

High-frequency vibrations (upper subliminal), 500–1,500 cps (studied by Mannheimer, Rodbard, Luisada, and others).

In this symposium are collected several studies, of two different types:

Technical studies, which establish the physical basis of phonocardiography (Zalter *et al.*); suggest a rational, technical approach to the construction of an apparatus (Luisada and Zalter); describe the scanning of the various bands by either spectral analysis (McKusick) or selective filtration (Friedland and Jacono); discuss new methods of study of the low-frequency vibrations (Agress *et al.*; Rosa); and give suggestions for the notations of phonocardiographic tracings (Luisada).

Clinical contributions based on phonocardiographic tracings; these include the studies of Werbin, and Luisada *et al.*, dealing with "functional" diastolic rumbles; Holldack's study of friction rubs; the study of Bleifer *et al.* of the systolic snaps; Eddleman's study of the ultra-low-frequency tracings (chiefly in coronary cases); Rivero Carvallo's study of the tricuspid murmurs in the combined lesions of the mitral and tricuspid valve; and Szatkowski and Schwied's study of murmurs erroneously attributed to congenital shunts.

It is fair to say that the contribution of McKusick on "relative" tricuspid stenosis partly belongs to the latter group of studies.

Therefore, contributions are of both a theoretical nature—discussing the physical, physiologic, and technical bases of phonocardiography—and a clinical type, which bring to light some of the practical applications of this method. It is a sign of our times that even "pure" clinicians like Rivero Carvallo, nowadays like to document their findings by means of phonocardiography instead of relying on subjective statements.

One might question whether "phonocardiography" should actually include the two marginal fields of inaudible cardiac vibrations, the

lowest (inaudible because the vibrations are too low-pitched) and the highest (inaudible because the vibrations are too small). The problem is largely one of semantics and can be solved by calling "cardiac infrasounds" and "cardiac ultrasounds," respectively, the two bands adjoining the one clearly perceived by the human ear. The definite unity of the vibratory phenomenon of the chest wall requires inclusion of these extreme bands. A new name might be suggested, *vibrocardiography*, even though its acceptance would require a change of traditional terminology.

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Phonocardiography

I. General Principles and Problems of Standardization*

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MODERN PHONOCARDIOGRAPHY, unlike modern electrocardiography, had to await the invention of the amplifying triode by Lee De Forest[1] in 1906. It was not, however, until the late 1920s that amplifier units for audio work became commercially available.[2–5] In contrast to electrocardiography, electronic amplification of the vibratory signals in the high-frequency range is essential, if sound phenomenon is to be studied and registered in its entirety. Whereas the mean instantaneous vector of the action potentials of the heart is of such magnitude that it can be clearly registered by a galvanometer of sufficient sensitivity,[6] this is not the case in phonocardiography. In the high-frequency range, the magnitude of the signal is such that extreme amplification becomes imperative.

Einthoven's registration of the ECG has thus remained virtually unaffected in principle through the advent of electronic amplification. The application of the same technique to phonocardiography,[7] however, resulted only in the registration of those vibrations whose magnitude is large enough to match the sensitivity of the galvanometer. As such, the limitations of the system are evident in the final record. In view of the range of magnitudes involved, simultaneous registration of the various vibrations, though theoretically feasible (assuming that the degree of amplification is made to suit the individual vibrations), is in practice well nigh impossible without some modification or alteration of the total signal.

This inherent difficulty in registration, and the necessity of introducing an element of linear distortion, was realized early.[5] Throughout the world, various authors applied themselves to the problems involved in the practical registration of the vibratory phenomena in their entirety.[8–18] Their success in overcoming and solving, more or less, the practical difficulties involved, is apparent through the variety of phonocardiographic systems in use.

The main problem in phonocardiography is not a new method of approach, but a critical evaluation and standardization of the existing systems.[19,20] The diversity of the methods employed in the various systems and the multiplicity of factors involved in any of them has now rendered the problem of standardization of critical importance. Insofar as the final tracing is a function of the technical factors involved in the system, their exact delineation and definition should be specified before trying to compare two tracings obtained through a different system.

In view of the above considerations, the authors' objective is twofold:

(1) They plan to re-examine and restate critically:
   - (a) Nature and scope of the phenomenon with which phonocardiography deals.
   - (b) Objective sought in studying this phenomenon.
   - (c) Possible methods of approach.
   - (d) Instrumentation and design factors bearing on the final record.
   - (e) Appraisal and critical analysis of existing systems.

(2) Through the design and construction of two different systems and the modification of a current system they plan to demonstrate the bearing of the above-mentioned factors on the final configuration of the tracing.

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Nature and Scope of Phonocardiography

THE VIBRATORY PHENOMENON

The total displacement of the chest wall over the precordial area constitutes a *periodic, complex waveform* of definite configuration and magnitude for a person under basal conditions.[22–31,65] This periodic waveform represents the complex of the vibratory phenomena reflecting the dynamic action of the heart.[29] As such, it represents the additive result of a finite number of pure sinusoidal waves of different amplitudes and frequencies. It can be mathematically proved that, no matter how complex a waveform is, it can always be analyzed and separated into a number of *sinusoidal components* comprising the harmonics and overtones of the fundamental frequency (Fourier's analysis).[32,41–44] When plotted on a frequency scale, a *continuous spectrum* of the frequency components will be inscribed. On the other hand, a truly periodic complex waveform, whose basic repetitive pattern can be superimposed and exactly matched to any other, can be analyzed and separated into *harmonic components* of the fundamental frequency if the sample tracing is long enough to be considered as extending to infinity. When plotted on a frequency scale, the harmonic components form a discrete set of lines which comprise a *line spectrum.*

If the periodic waveform is measured over a finite extent (a limited number of cycles), then it is not truly periodic any longer, and overtones will be introduced; the spectrum then is necessarily continuous. Although successive heart beats cannot be considered exactly identical, the repetitive character under basal conditions is close enough to approximate a truly periodic waveform. Under such circumstances, the frequency spectrum of the complex waveform can be said to approach a line spectrum. It must be stressed that *the periodic complex waveform inscribed by the displacement of the chest wall constitutes a single physical entity;* its energy content is similarly equivalent to the total energy appearing across the chest wall, since it incorporates the energy level of all the component sinusoidal waves.

The spectrum of vibrations generated by the heart beat and transmitted through the tissues to the body surface overlaps only partly the auditory perception area (Fig. 1). The subdivision of the spectrum into auditory and infrasonic bands is, therefore, necessarily imposed by the physiologic limitation of the auditory system of man and not through any physical difference of the phenomenon under consideration.

PHYSICAL DIMENSIONS OF THE FREQUENCY SPECTRUM

In the opinion of the authors, the vibratory spectrum can arbitrarily be subdivided into two main adjacent bands. Since the lower limit of auditory perception is generally considered to be about 20 cycles per second (cps), this frequency can be considered as a dividing point separating the spectrum into an *auditory* and an *infrasonic* band.[33] Furthermore, the frequency components comprising the auditory band can be further subdivided into two adjacent bands in its relation to the threshold of audibility.[34] The first subdivision, extending from 20 cps to roughly around 40 cps, is made of vibrations of high intensity; nevertheless, the energy level of these components is not high enough to compensate for the extremely low sensitivity of the

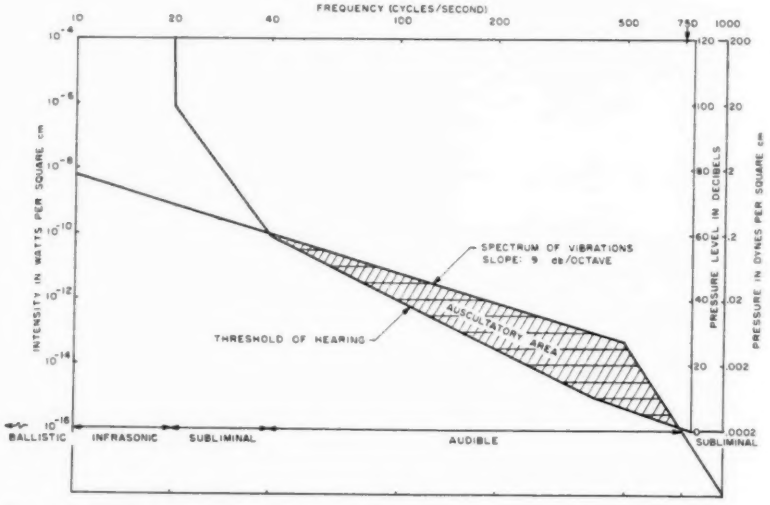

FIG. 1. Schematic representation of the vibratory spectrum in relation to the threshold of hearing.

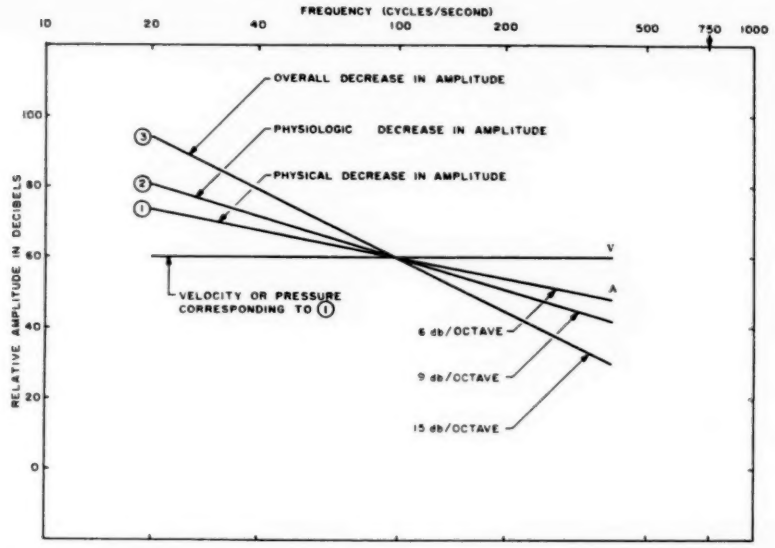

FIG. 2. (*1*) Decrease in amplitude with increase in frequency for constant velocity. (*2* and *3*) Physiologic and over-all decrease in amplitude with frequency.

human ear in this range. This band is therefore either inaudible or barely audible, according to the intensity of the vibrations and the individual threshold of the observers. The authors suggest the name of *lower subliminal band* for these vibrations. The second band extends from 40 to 1,000 cps and comprises components of still less magnitude; however, as the threshold of hearing over this band is relatively high, i.e. the ear is more sensitive, these frequency components, as perceived by the normal human ear, constitute the audible portion of the vibratory spectrum (audible band).

In the range above 1,000 cps, the ear is still amply able to perceive vibrations. However, due to the natural decline in amplitude, vibrations of greater and greater frequency have a proportionally smaller and smaller magnitude. Therefore, if vibrations above 1,000 cps are created by the heart,[47] they will be inaudible, not because of undue frequency, but because of poor intensity. This upper band should be termed *upper subliminal band*.

Of the total vibratory spectrum, therefore, only a limited band lends itself to auditory perception; what the average listener hears in auscultation of the heart is usually restricted to the above band, between 40 and 1,000 cps. Evidently, auscultation is far from being a perfect instrument for the assessment of the total vibratory spectrum. Furthermore, as an element of linear distortion is naturally introduced by the ear in auditory perception (sensitivity for higher frequencies increases on a logarithmic scale), an objective analysis and evaluation of the audible part of the spectrum is impossible by the unaided ear.

The infrasonic band includes, besides the fundamental frequency,* those harmonics† (± overtones‡) which form the lowermost frequency components of the spectrum. It is this band which accounts for the major portion of the vibratory energy appearing across the chest.

The nature of the infrasonic vibrations appearing at the surface of the chest wall needs further consideration. These vibrations have been the object of numerous studies and observations.[26–28] Johnston and Overy[29] pointed out the dual nature of these vibrations in their effort to record exclusively the low-frequency band of the vibratory spectrum. In essence, two superimposed patterns of motion are inscribed by the

* *Fundamental frequency* is the lowest component frequency of a periodic quantity. It is equal to the inverse duration of the waveform periodic pattern. Thus, for a "linear" phonocardiogram (apex cardiogram) whose period (time interval of one cycle) equals 0.8 sec, the fundamental frequency is 1/0.8 or 1.25 cps or 75 cycles per minute, which corresponds to the heart rate. This is to be differentiated from the resonant frequency, which is of the order of several cycles for the heart and chest wall.

† *Harmonic* is a frequency component which is an integral multiple of the fundamental.

‡ *Overtone* is a frequency component, higher than the fundamental, which is not necessarily an integral multiple of the latter.

chest wall: (1) The whole body including the chest wall oscillates with an absolute movement in regard to a fixed point in space; this movement, which roughly constitutes the ballistic component, naturally falls into the lower frequency range. (2) Superimposed on the above is the vibratory or harmonic motion of the chest wall which, in contrast, bears a constant relationship to a fixed point in space, and comprises the lower end of the vibratory spectrum, with which we are concerned. This distinction is important if we wish to extend our analysis and registration of the vibratory phenomena in their totality as they appear on the chest wall, irrespective of their genesis.

Intensity Level of Frequency Spectrum: A gross evaluation of the intensity level of the different bands has revealed a tendency to decrease with increasing frequency.[41,42] From the available published figures and our own unpublished data, the intensity level of the spectrum can be shown to decrease at a rate of 6–12 decibels (db)* per octave (*physiologic decrease*). Stated differently, a frequency component at 200 cps has an intensity level which is on the average 9 db lower than a 100 cps component. In transducing sound pressures into galvanometric deflections (amplitude or displacement), the *physical factor* has also to be taken in consideration if accurate analysis and calibration are required, because, for a given pressure, the amplitude decreases with increasing frequency.† This is demonstrated in Figure 2, where the horizontal line represents the pressure or velocity, while the sloping line is the amplitude. Translated into decibels, the amplitude of a sinusoidal wave is said to decrease at the rate of 6 db/octave for constant velocity. Taking note of the above factor, and adding it to the physical factor, the amplitude of the frequency spectrum can then be shown to slope instead at the steeper rate of from −12 db/octave to −18 db/octave, corresponding to an inverse relation from the second to the third power of the frequency.

The dynamic range of amplitude covered by the frequency spectrum over a band of three decades (i.e., 1 to 1,000 cps) amounts to 120 db, assuming a sloping amplitude of 12 db/octave or 40 db/decade.[36] It is thus logical to assume that the vibratory spectrum in its entirety constitutes a unified field whose subject matter pertains to the technique of phonocardiography.

* db is the symbol of the decibel. A decibel is one-tenth of a bel. A bel is a unit on the logarithmic scale, used for determining the logarithmic ratio of two quantities to the base 10.

† This derives from the formula $A = pmax/2\pi fZs$, where A is the amplitude, p the pressure, Zs is the impedance, and f the frequency.

Objectives of Phonocardiography

It is unfortunate that the prefix "phono" is usually employed in reference to the "audible" portion of the spectrum, so that "phonocardiography" is generally thought to be synonymous with the graphic registration of the auscultatory phenomena. On the other hand, "sound" is a physical phenomenon, whether or not it is "audible" or "heard." The authors suggest to define phonocardiography as *the graphic registration (quantitative and qualitative) of the total vibratory spectrum with or without attenuation of any band.* As such, phonocardiography should include the study of (1) the infrasonic band, (2) the lower subliminal parts of the auditory band, (3) the audible components of the auditory band, and (4) the upper subliminal parts of the auditory band. However, no system of phonocardiography can *simultaneously* register the various adjoining bands with equal clarity and detail;[13] moreover, it is imperative to attenuate the infrasonic band in order to register the auditory band, and, on the other hand, it is necessary to sacrifice a detailed definition of the auditory band in order to obtain an exact transcription of the total spectrum. Therefore, different terms should be applied to the selective registration, on the one hand, and to the faithful undistorted recording of the periodic complex waveform on the other, notwithstanding the essential unity of the whole phenomenon.

Having thus defined the extent and scope of the phenomena under consideration, it becomes apparent that the objective in any proposed mode of study resolves itself simply into *the complete scanning of the total spectrum*, first for detection and isolation of extraneous harmonics or overtones which may be missed or otherwise go unnoticed and, second, for a quantitative evaluation in regard to both their absolute or relative intensity.[46]

Possible Methods of Approach

Given the physical dimensions and the dynamic range of the vibratory spectrum (60–120 db of pressure range over 1,000 cycles), the difficulties involved in linear registration are self-evident. The ear is admirably suited to cope with such a range of intensities, since audition is submitted to a special distortion—a logarithmic increase in intensity is perceived

linearly.[33] The dynamic range of the ear being 130 db, the upper part of the vibratory spectrum of the heart is well within its range. A transducer, on the other hand, is basically a "linear" device, so that the electromotive force (e.m.f.) generated is a direct function of the pressure or displacement of the frequency components.[37] The dynamic range that can be recorded by such a system is physically limited by the paper width to a ratio of 10:1 or 20 db in regard to voltage. Therefore, a linear system is unable to contain the spectrum in its totality and, at the same time, retain a measure of clarity and detail for the individual vibrations in the high-frequency range.

Methods for Clear Registration of High-Frequency Components: Such a tracing, while inadequate for the study of the high-frequency components of the auditory band, is nevertheless "linear" and represents accurately the complex waveform which constitutes the total vibratory spectrum. *It is evident that any attempt to register with clarity the high-frequency, low-intensity components would require the attenuation of the low-frequency components.* Two methods readily suggest themselves. Both involve the attenuation of the low-frequency components, but differ in their relative approach to the problem:[45,46]

(1) A form of frequency correction or compensation (known as equalization) may be employed in order to obtain uniform recording characteristics throughout the spectrum. The insertion of an equalizer in the circuit at a specific turnover frequency of the same but opposite slope would reduce the spectrum to a flat frequency characteristic by attenuating the low frequencies below the turnover frequency and boosting the frequencies above it. The converted spectrum can then be linearly amplified to any desired level. The final tracing, though distorted, reproduces with equal clarity and amplification all the frequency components of the total spectrum.

(2) The frequency spectrum can be subdivided into adjoining bands through the use of *high-pass* or *band-pass filters*. The band passing through the filter is then amplified to the desired level for recording. Evidently, the bands in question should cover the entire frequency spectrum if a complete scanning is desired.

Instrumentation and Design Factors Bearing on the Final Record

These factors include the transducer device, the equalizer or filter circuit, the amplifier, and the recording system.

THE TRANSDUCER

The microphone is the critical element in the phonocardiograph because it is the device employed for converting the energy contents of the vibratory spectrum into electric pulses of a certain voltage.[36–38,40] An ideal microphone should have a voltage output which is a faithful undistorted image of the pressure variation at the input. Both linear and nonlinear distortions must be kept low, while extraneous or interfering vibrations must be reduced to a minimum.

Microphones used in phonocardiography convert the vibratory motion of the chest wall either directly or indirectly into deflection of a diaphragm, coil, or ribbon.[38] In the *indirect method*, a closed air chamber is interposed, so that the displacement is transformed into pressure, which then acts on the diaphragm. In the *direct method*, the diaphragm is brought into direct contact with the skin through a connecting rod. An original approach recently described by Groom[59] attempts a perfect capacitive coupling by juxtaposing the skin to a capacitor plate.

Both the mode with which the deflection of the diaphragm is converted into e.m.f. and the particular aspect of the vibratory energy to be transduced (displacement or pressure vs. velocity as a measurable dimension of a sinusoidal wave) determine the electrical behavior of the microphone.

In the piezoelectric crystal and the capacitor microphone, the e.m.f. generated at any given moment is directly proportional to the deflection of the diaphragm, which in turn is a function of the pressure applied at the input. In both cases, the design of the microphone is such as to insure that the ratio of the deflection to the pressure applied is independent of frequency.[21] In the final analysis, both the crystal and the capacitor microphones are displacement microphones. The displacement of the diaphragm, however, is greatest for the low-frequency components, since for a given pressure the amplitude decreases with increasing frequency.

Frequency-Response Characteristics of Different Microphones: Given two vibrations of equal pressure (e.g., 100 cps and 200 cps), the amplitude (displacement) of the higher is one-half that of the lower. In other words, the higher frequency vibration completes a

full cycle in half the time required by the lower. The particle velocity is then the same for both. Pressure being equal, it follows that the amplitude of vibration is inversely proportional to the frequency, while the velocity is independent of the frequency. This is demonstrated in Figure 2, where the horizontal line represents the velocity and the sloping line the amplitude. Translated into decibels, the amplitude of a wave can be shown to decrease at the rate of 6 db/octave for a constant velocity. Then, if the microphone response is linear, the deflection of its diaphragm will be proportional to the amplitude of the wave. To recapitulate, both the *crystal* and the *capacitor microphones* transduce displacement into e.m.f. since the static pressure developed in the closed chamber is a function of the skin displacement which it circumscribes. Line *A*, then, is the fundamental response characteristics of both the piezoelectric and the capacitor microphones.

In the *dynamic microphone*, the diaphragm is similarly brought into motion by the varying pressure within the closed chamber; however, the diaphragm in this case carries a conductor or a coil which is placed in a constant magnetic field. The e.m.f. generated is then proportional to the velocity of the diaphragm or coil deflection, which in turn is proportional to the product of the distance times the frequency. If the response is to be linear at all frequencies, the relationship between the velocity of the vibrating system (diaphragm-coil) and the pressure must be independent of frequency. Hence, line *V* is the response characteristic of the dynamic microphone. The tracing is then a record of the vibrational velocity, which is the derivative of the displacement (amplitude) of the vibrating surface. Both types, therefore, respond to pressure, but the method by which they convert it to voltage determines the response characteristics (velocity vs. displacement) of the respective microphones.

EQUALIZERS AND FILTERS

The response characteristics of any phono system is a function of those of the filter or equalizer placed in the circuit. Essentially, this is determined by the extent and degree of attenuation to which a specific range of frequencies is submitted. Therefore, familiarity with the basic response characteristics of these units is essential for an intelligent evaluation and recording of the vibratory spectrum.

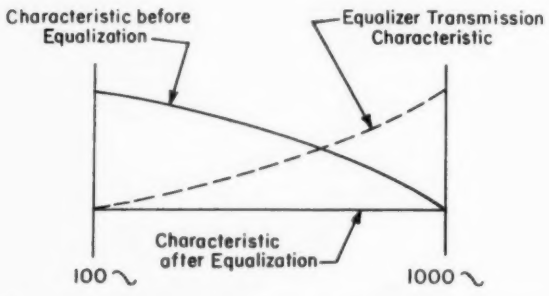

FIG. 3. Frequency characteristics of vibratory spectrum before and after equalization.

Equalizers

Definition: Basically an equalizer is a device for altering the frequency characteristics of a recording system.[36,38,40] This is achieved by increasing or decreasing the frequency response in any segment of the frequency spectrum. An equalizer may be considered a variable-loss device, controlled by the applied frequencies, which in turn vary the gain of the phono system in a given frequency range. Thus, if several frequencies are simultaneously applied to the input terminal of an equalizer, their amplitude relative to each other will be altered at the output of the equalizer depending upon the characteristics of the latter. The effect of equalization on the frequency characteristics of the vibratory spectrum is illustrated in Figure 3. Inserting in the circuit an equalizer having frequency characteristics inverse to those of the vibratory spectrum would restore the spectrum to a flat frequency characteristic. However, in so doing, the over-all signal level would be lowered by an amount approximately equal to that inherent in the properties of the equalizer (insertion loss). The signal may then be returned to its original level by inserting an amplifier (having a gain equal to the equalizer insertion loss) after the equalizer network. The amount of loss will depend on the degree of equalization. It is customary to refer to the insertion loss with respect to a specific reference frequency.

Types: Normally, equalizers are composed of circuit elements consisting of resistor,

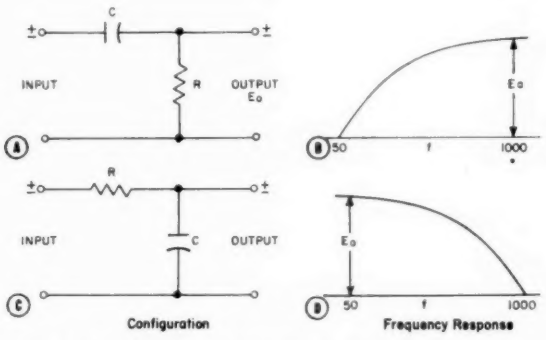

FIG. 4. (*A*, *B*) RC high-pass filter. (*C*, *D*) RC low-pass filter.

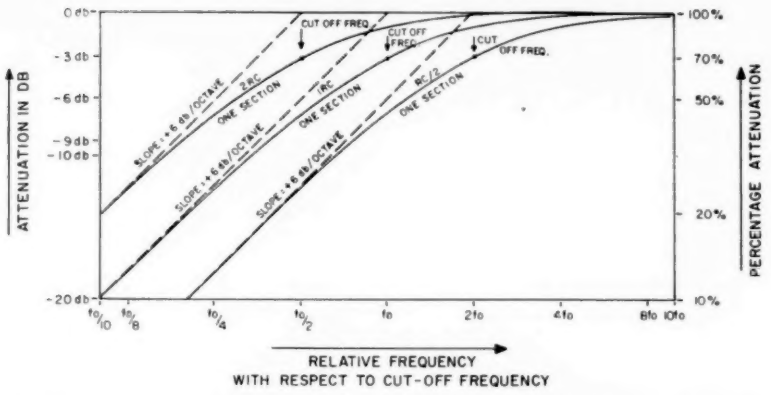

FIG. 5. Relative voltage attenuation of a one-section RC filter. Note how doubling RC shifts cut-off frequency down by one octave and halving RC shifts cut-off frequency up by one octave with respect to filter of time constant RC.

inductor, and capacitor that are connected according to a definite configuration and specific types. The elements composing these configurations offer an impedance to certain frequencies and thus control the frequency response of the equalizer.

Simple Equalizers—RC Types: It is possible to obtain many different types of frequency correction by the use of networks containing only resistor and capacitor, either of which may be fixed or variable in value. Practically all such circuits are based on or are comparable to simple low- or high-pass filters and employ only two reactive elements, *resistor* and *capacitor*. Figure 4 illustrates simple high- and low-pass filters and their typical curves. If a single voltage of constant amplitude is applied to the input terminals of the circuit in Figure 4*A* and the frequency of that signal is varied from 50 to 1,000 cps, the output voltage E_o will *increase* as the higher frequencies are approached; this is evident from the characteristic curve (*B*). On the other hand, if a signal voltage of constant amplitude is supplied to the input terminals of the circuit in Figure 4*C*, while the frequency is varied from 50 to 1,000 cps, the output voltage E_o will *decrease* (Fig. 4*D*) as the frequency is increased, because the reactance of the capacitor varies inversely with frequency.

To understand how the frequency characteristic in Figure 4*A* and *B* is obtained, it must be remembered that a noninductive resistor offers the same resistance at all frequencies and also that, because of its reactance, a capacitor offers greater opposition at the lower frequencies than at the higher ones. Therefore, in the circuit of Figure 4*A*, as the frequency increases, less and less opposition is offered by the capacitor, until finally it is out of the circuit for all practical purposes. The circuit of Figure 4*C* operates in an inverse manner to that of Figure 4*A*.

Further discussion of the types of possible equalizers and their design and circuit characteristics is beyond the scope of this paper. However, since the frequency response of a phono system is of paramount importance, if the final record is to be correctly evaluated, a more detailed analysis of the frequency response of a simple RC filter is desirable; the more so as the principles involved are common to all equalizers and filters. This is best understood by reference to Figure 5, illustrating the over-all frequency response obtained with a single-section high-pass RC filter. The cut-off frequency is defined as the frequency at which the response is down 3 db or 70 per cent below maximum.* At a frequency which is 10 times or a decade higher than the cut-off frequency, the insertion loss is only 0.01 db. On the other hand, at a frequency one-tenth that of cut-off, the insertion loss is 20 db, or only 10 per cent of the original. Beyond 10 times the cut-off frequency and below one-tenth of cut-off, the response, when plotted on a logarithmic scale, becomes linear with frequency. The slope or rate of attenuation in the first instance is 0.1 db/octave and, in the second, −6 db/octave. Between these two points, the filter response is nonlinear (as can be seen from the graph), and the rate of attenuation is a function of the instantaneous slope, which is the slope of the tangent at that point. Half-way

* This is a direct inference from the design formula $f_c = 1/2\pi RC$, where f_c is the frequency of 3 db loss, R the circuit impedance, and C the value of the capacitor.

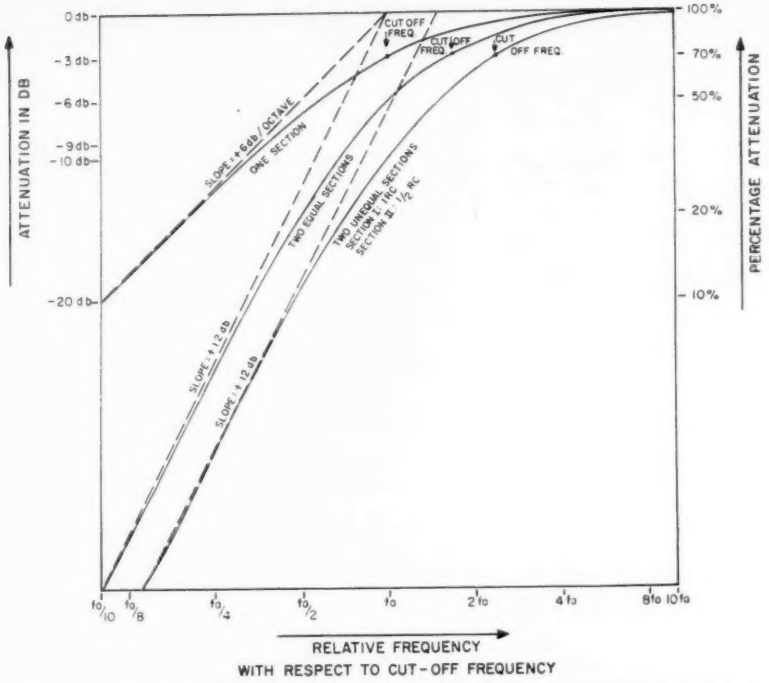

FIG. 6. Relative voltage attenuation of two-equal-section RC filter and two-unequal-section RC filter.

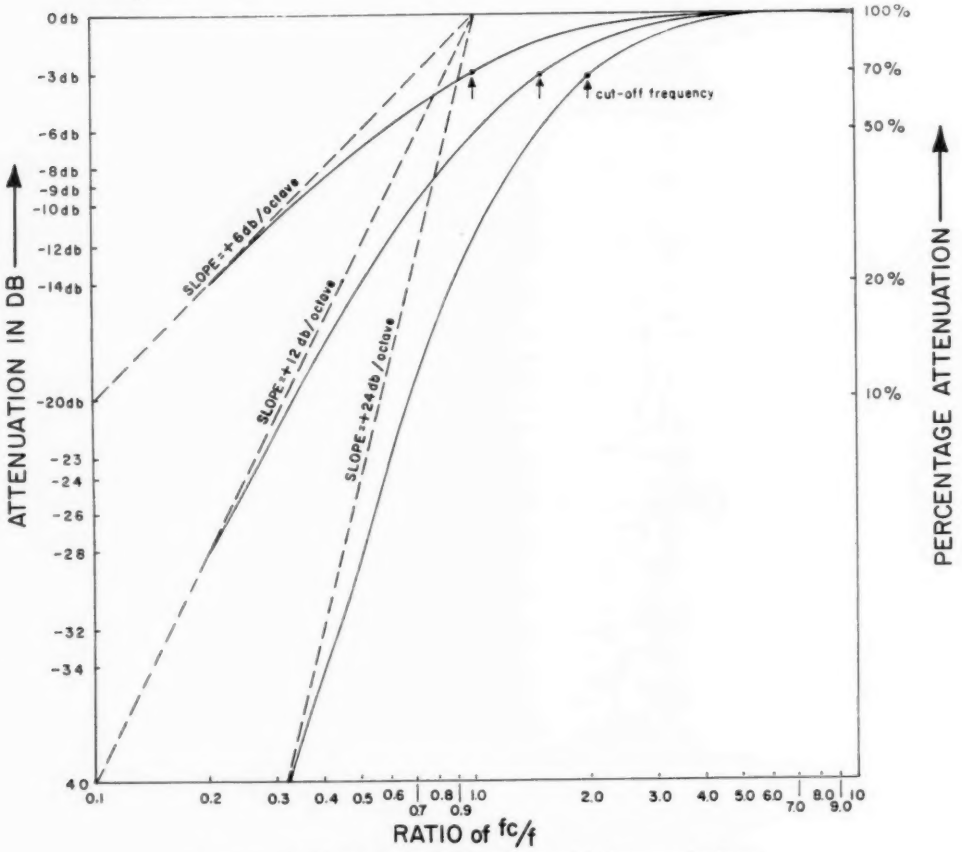

FIG. 7. Shifting of cut-off frequency with increase in slope.

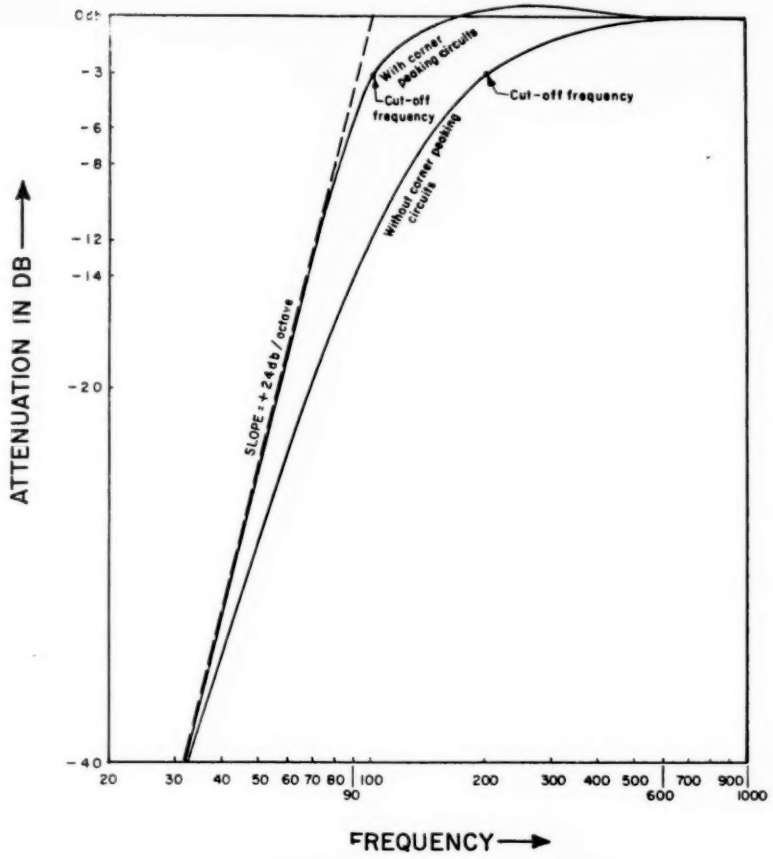

FIG. 8. Effect of peaking circuits on cut-off frequency.

between the 100 per cent and the 10 per cent points, the slope is only −3 db/octave, or one-half the attenuation rate. Quantitatively, the attenuation to which a particular frequency is subjected can be read directly from the characteristic curve in decibels below the 0 db level.

Since the frequency response above or below cut-off is critical, the latter characteristic bears directly on the frequency response of a photo system.

When two or more RC sections are connected in tandem, the cut-off frequency shifts from the midpoint because it is by definition the point of 3 db attenuation (Fig. 6). The rate of attenuation becomes also steeper, as the effect is cumulative (Fig. 7). However, in the design of multiple-section RC filters, the cut-off point can be made the same for different attenuation rates.

It should be realized that the use of RC types of equalizers and filters for the purpose of frequency correction is not restricted to specific circuits outside the amplification stage; on the contrary, their use within the amplifier circuit provides a frequency response to suit any one purpose. This being so, the frequency response of an RC coupled amplifier is a function of the RC coupling at both ends of the middle band; above and below the middle band, the attenuation characteristic is essentially that of an RC filter.

Filters

Definition: A filter is a network whose function is to pass a given band of frequencies without appreciable attenuation and to attenuate all others. The frequency which marks the junction of a pass band and an attenuation band is known as the cut-off frequency. From the standpoint of frequency characteristics, filters are essentially of three types: (1) low-pass filters, (2) high-pass filters, and (3) band-pass filters. In the low-pass filters, *all frequencies above cut-off frequency are attenuated* at a specified rate; in the high-pass filters, *those below a cut-off frequency are attenuated;* a band-pass filter *allows a particular band of frequencies only.* The desired effect is usually obtained by combination of high- and low-pass filters.

LC Filters: The design of LC filters consisting of reactive elements (capacitors and inductors arranged in a specific configuration) is beyond the scope of this paper. LC filters have been used in phono systems with good results; however, they have certain drawbacks that can prove critical, since the inductance necessary to handle the low frequencies can be large and hence tend to pick up interference unless a careful screening is obtained. A second undesirable feature is the considerable phase variation with frequency within the pass band.

High-Pass and Low-Pass RC Filters: RC filters[38,40] are particularly suited for biologic work involving vibration studies and in conjunction with any low-frequency phenomenon involving selective amplification. The frequency response of simple RC filters has been discussed. Filters, either high or low, can be constructed by simply coupling two or more cascaded resistance-capacitance elements. Since the rate of attenuation of each RC element is 6 db/octave, the net attenuation rate is a function of the number of elements cascaded. Four RC elements would then produce an attenuation rate of 24 db/octave (see Fig. 7). The cut-off frequency of such a filter does not correspond to the point at which the slope of the asymptotic filter intersects the zero db gain; instead, it has been shifted to the right, because by definition the cut-off frequency is the frequency at which the output of the filter is 3 db down from the output at the pass band. This can be corrected by the introduction of a peaking circuit in order to sharpen the corners of the pass band characteristic; i.e., in order to increase the slope of the corner frequencies (Fig. 8). A circuit with a peaking factor slightly greater than 0.6 reduces the attenuation at the corner frequency by approximately 9 db. Simultaneously, it introduces a gain peak in the pass band by approximately one octave above the low cut-off frequency and one octave below the high cut-off frequency of 0.75 db. The cut-off frequency is then the frequency at which the extension of the straight portion of the filter attenuation slope (24 db/octave) intersects the extension of the band-pass gain characteristics. At the cut-off frequency, the slope is approximately 12 db/octave and, at the 12 db point, the slope has essentially reached its nominal value of 24 db/octave.

The performance of such a filter in conjunction with phonocardiographic studies is far superior to that of a 24-db 4-stage filter with unity peaking factor, because of the increased gain near the corner frequency. Thus, it has been possible to reduce and practically eliminate that feature of the filter characteristic (i.e., the curved upper critical portion) which was difficult to circumvent. Furthermore, if sufficient amplification is used in order to overcome the loss in the filter, the over-all attenuation from input to output can be made to approximate zero db in the pass band.

Band-Pass Filters: A band-pass filter is essentially made of a high-pass and a low-pass filter connected in series. Such a filter should incorporate the characteristics of both the high- and the low-pass sections.

In the operation of a band-pass filter, the interaction of the peaking circuits of both the high and low cut-off should be taken into consideration. For a pass band of one octave, however, it should be possible to obtain a pass band with zero db in the center and a 3 db loss at the cut-off.

THE AMPLIFIER

An amplifier is a device whose main function is to magnify and reproduce the essential features of an input wave representing very little energy.[39] Since the output represents an appreciably greater amount of energy, the amplifier draws power from a source other than the signal. The fundamental principles of vacuum-tube amplification and design factors need not be elaborated here, as they are well known. On the other hand, the design or selection of an amplifier particularly suited for phonocardiographic work requires great attention to those desirable characteristics and specifications which have a direct bearing on the amplified signal. Amplifiers can be broadly classified into separate classes, depending upon the region of the tube characteristics in which they operate. When the operation is *linear* (i.e., restricted to the linear region of the tube characteristics), the input and output voltages are linearly related and the amplifier is designated as class A amplifier.

Partial operation of the tube in the nonlinear region during a given fraction of the cycle length results in an output waveform which is not an exact reproduction of the signal. Such an amplifier cannot be considered a linear device, as it results in waveform distortion. Generally, it is designated as class AB, B, or C, depending on the degree of nonlinearity incurred.

Considering the intensity of the signal, the

amplification derived from a single stage of amplification may prove insufficient; recourse must be had then to connecting two or more stages *in cascade*. A coupling network is used to connect the separate stages. The type of coupling used in a *cascade*, or *multistage*, *amplifier* determines the range of frequencies over which the amplifier operates. Thus the frequency range over which an amplifier operates serves as another basis for the classification of amplifiers into audio frequency (16 to 2,000 cps), radio frequency (500 to 1,500 kc), and video frequency (30 kc–30 mc).

Finally, an amplifier may be designed with regard to its final stage: (1) as a *voltage amplifier*, intended to supply the largest practicable amplification or output voltage with minimal distortion; or (2) as a *power amplifier*, which has as its objective the development of as much energy as possible irrespective of voltage. A voltage amplifier intended to operate into a cathode-ray oscilloscope may be considered satisfactory. On the other hand, if the amplifier is to drive a loudspeaker or any other power-consuming device, power amplification is necessary.

Distortion: Ideally, an amplifier is supposed to produce an output waveform that duplicates exactly the input waveform in all respects except magnitude. Imperfections in the amplifier always cause some differences between the output and input waveforms. Such a deviation from the ideal is called *distortion*. This is better appreciated through the application of Fourier's analysis to the output and input waveforms. Since the amplifier input is a complex periodic waveform, such as constitutes the vibratory phenomenon of the heart, it can be represented (as mentioned earlier) by a series of sinusoidal components. For the amplifier to duplicate the waveform's original shape with fidelity, the individual frequency components have to be equally and faithfully amplified and their original time relationships preserved. An amplifier that fails to preserve the same relative amplitudes among the frequency components of the spectrum is responsible for frequency distortion, thus limiting the range of frequencies which it can satisfactorily handle. On the other hand, an amplifier which distorts the shape of the frequency components, as may arise from operating in the nonlinear region of the tube characteristics, is responsible for nonlinear or amplitude distortion. Since the output waveform is no more an exact replica of the input

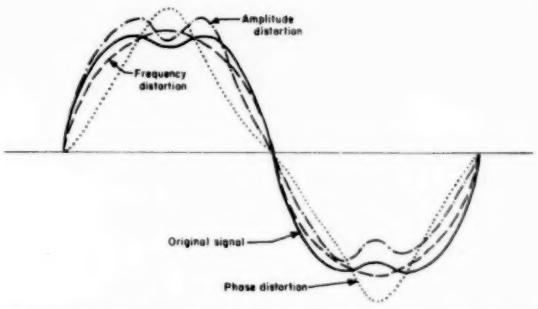

FIG. 9. The effect of distortion on a complex waveform (modification of Terman[40]).

waveform, it is obvious that Fourier's analysis of the former should contain harmonics or frequency components which are not present in the input wave and which therefore are artificially generated. Finally, if the amplifier fails to preserve the time relationship among the various components, the output waveform is said to suffer from phase distortion (Fig. 9).

Amplification or Gain: Voltage amplification or gain can be conveniently expressed by the ratio of the output voltage to the corresponding signal voltage. This factor is then a measure of the amplification. However, since the signal is in many instances a complex wave, gain for the various frequency components may not be the same, depending on their relative frequency position. A more accurate picture of gain for any amplifier can be obtained from the frequency characteristics or the frequency response curve which is a plot of the voltage gain vs. frequency. Logarithmic scales are used both for voltage gain and frequency. This is so because the ear discriminates among various intensities or frequencies more by their ratio than by their absolute difference and, on a logarithmic scale, equal ratios appear as equal increments. Gain may then be expressed in absolute numbers or in decibels voltage gain above the original input level of 0 db [this will be shown in Part III, Fig. 7*B*].

Amplifier Coupling: The type of coupling between any two stages of an amplifier determines to a large extent its frequency response characteristic. When it is desired to transmit steady d.c. potentials, or variation of less than 1 cps, *direct coupling* must be resorted to. Such a method of coupling, which offers a conductive path for the direct current from one stage to the other, results in a direct coupled or *direct-current amplifier*. For frequencies above 1 cps and where

the steady d.c. component of the complex waveform need not be transmitted or amplified (i.e., when the absolute energy contents or the intensity level of the wave as in pressure recording is not under study) an alternating current amplifier or *a.c. amplifier* is the unit of choice.

Several types of coupling can be used in conjunction with a.c. amplifiers, the relative merit of which depends on the frequency response desired and the degree of distortion tolerated.

RC Coupling: This is the simplest and most stable mode of coupling. The frequency characteristic of an RC coupled amplifier is determined by the capacitances and resistances in the circuit. Such a response presents a midband of constant amplification (flat frequency response over a determined range of frequencies), which drops off both at the high and low cut-off frequencies at the rate of 6 db/octave. Since both the low and high cut-off frequencies are a function of the total RC time constant for that frequency, the design of the amplifier can be modified to shift the cut-off frequencies along the frequency scale so as to include any desired range of frequencies in the midband of linear characteristic.

Transformer Coupling: A transformer may be used to couple any two stages of an amplifier. Voltage variation may then be transmitted without direct connection. It is often used to couple the transducer to the first stage (*dynamic microphone*). Transformer coupling can be actually advantageous for many reasons, not the least of which is a further voltage gain by using a step-up transformer. Its use in amplifiers for biologic work is not widely practiced, as it complicates amplifier design in order to avoid the distortion introduced by stray fields and on account of the poor frequency band covered. Furthermore, unless the transformer is properly chosen, a high-frequency peak in the amplifier frequency response is likely to distort the output at the resonant frequency (this will be further discussed in Part II).

Noise: Noise, as a constant by-product, can be considered as the limiting factor in the resolution capacity of a transducer-amplifier system. The noise level generated by such a system sets the minimal limit of the signal intensity which can be usefully transduced and amplified, no matter how many stages of amplification are added. It should be emphasized that the intelligence transmitted by the amplified signal is a function of its signal-to-noise ratio (commonly referred to in phonocardiographic parlance as *clear baseline*).[58] A signal whose intensity is slightly above, or similar to, that of the noise level does not lend itself to interpretation, as it is completely masked by the ambient noise. When the output of an amplifier (in the absence of a signal) is fed into an oscilloscope, it appears as a series of spikes of varying size. From the known gain of the amplifier, the magnitude of the signal which would give a similar deflection as the noise can be calculated. Furthermore, since the fluctuations are random, their frequencies are distributed evenly over a very wide band of several megacycles of the frequency spectrum. As a result of this wide distribution, the noise level at the output becomes a function of the band width being recorded; limiting the band width to the frequency spectrum of the signal under study will improve the resolution of the amplifier by increasing the signal-to-noise ratio at the output. This fact becomes of great importance when dealing with signals of small intensities that require great amplification.

THE RECORDING OSCILLOGRAPH

The recording oscillograph represents the final, or transcription, stage of the phono system. The small current and voltage variations which are transduced, amplified, and filtered are then transferred to a photosensitive record (via the oscillograph) where they can be measured and studied individually and comparatively. Recording oscillographs in use incorporate as the recording arm either a *cathode-ray tube* or a *galvanometer*.

Cathode-Ray Tube: The cathode-ray tube is undoubtedly the most accurate and sensitive recording device. Unlike all other means of recording, it is free from the effect of inertia, and hence *its frequency response is unlimited.* In conjunction with a blue fluorescence of high actinic value it is ideal for photography, since a slow paper can be used with good results. In conjunction with a phonocardiographic system, however, the cathode-ray tube may prove less than ideal because of the limitation on the brightness of the spot when high-frequency vibrations are being inscribed, since the faster the spot moves, the fainter the trace becomes. The use of fast lenses can only partially compensate for the limitation of the writing speed. Increasing the accelerating potential on the anodes, and thereby increasing the velocity of the electrons, can be used with good effect, provided a means

for modulating the brightness is also included. Such an arrangement, however, lowers the sensitivity of the "gun." The use of an *electronic switch* for multiple recording (see below) further detracts from the clarity and resolution of the record in the high-frequency range. The use of the more expensive double-beamed tubes with two separate "gun" assemblies could obviate this drawback, if properly synchronized (something which seems difficult to achieve). Multiple-beam tubes are, however, commercially unavailable.

Oscillographic Galvanometers: Recording oscillographs incorporating moving-coil galvanometers or modifications thereof are commonly used in conjunction with amplifying circuits for recording both low- and high-frequency vibrations. The string galvanometer, perfected to a high degree of sensitivity and frequency response prior to the advent of modern electronics, seems to have been relegated to a specialized usage by subsequent developments.[70] Discussion of the basic theory of oscillograph galvanometers is beyond the scope of this study. Nevertheless, familiarity with this theory, particularly in regard to damping and its relation to frequency response, is of great value in the application of galvanometers to a specific use. Various principles have been employed in the design of galvanometers.

The moving-coil, or D'Arsonval, galvanometer is the most common. The moving element in this type consists of a coil of fine wire suspended between taut suspension strips and mounted in a strong magnetic field. Current is conducted to the coil through one strip and out through the other, causing the coil to turn and twist the strips. The mirror is mounted on the coil. Such an arrangement can be compared to an elastic system with an instantaneous deflection which is at all times proportional to the result of the forces acting upon it at any given instant.

The moving-coil galvanometer may not be as accurate as the cathode-ray tube as far as flat frequency response and phase relationship are concerned, but, when properly chosen to cover the desired range of frequencies and damped accordingly, the resultant tracing is superior to that of a cathode-ray tube in resolution, clarity, and time of exposure and is accurate enough for most practical applications. Furthermore, by using a multielement magnet block, a large number of elements can be compressed in a small space for multiple recording. In the opinion of the authors, the moving-coil galvanometer (or its modifications) is today, pending the development of a compact multiple-gun cathode-ray tube, more suitable for phonocardiographic practice than any other recording device.

Summary

The general laws of auscultation and the basic principles and scope of phonocardiography are analyzed and discussed with particular reference to instrumentation. The characteristics and responses of the various types of transducers (microphones), equalizer or filter circuits, amplifiers, and recording oscillographs are presented; they must be known for proper clinical application of phonocardiography.

(*References for this article appear at the end of Part III, p. 38*)

Phonocardiography

II. Appraisal and Critical Analysis of Existing Systems*

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IT IS A CREDIT to human ingenuity that phonocardiographic systems throughout the world have been exhaustive in their application of the various design factors to phonocardiographic apparatus based on electrical methods. This plethora of ideas has been a positive element in the development and refinement of phonocardiographic technique. However, one cannot lose sight of the negative aspects because, after some 30 years of engineering practice, the design and characteristics of phonocardiographic apparatus are still a matter of individual predilection and choice. This can be partly attributed to the complex nature of the vibratory phenomena, in contradistinction to that of the electrocardiogram. A major obstacle was represented by the practical difficulty of devising a transducer of sufficient linear characteristic to embrace the total spectrum. The limitation of the individual separate stages is another. Nevertheless, these practical considerations aside, there is room within the existing framework to improve and probably to standardize some of the more salient features whose value can no longer be contested.

The Committee on the Standardization of Phonocardiography has done a great deal in the effort to place phonocardiography on a broader scientific basis.[55–57]

In the following discussion, the authors will try to survey the systems of phonocardiography which are presently employed in America and Europe, with particular reference to their frequency (or response) characteristics (Table I). This discussion is partly based on first-hand experience with various apparatus, and partly on published data or personal communications. This, however, is not complete, since in many instances the available data are scanty.† Even so, this critical analysis is justified if one wishes to proceed further in formalizing the necessary standards and improving on existing designs. The evaluation shall be confined to apparatus based on publications accepted as original and basic.

SANBORN PHONOCARDIOGRAPH

In the United States, the Sanborn Twin-Beam and its predecessor, the Stetho-Cardiette, have pioneered in the field of clinical phonocardiography. Based on the comprehensive and original work of Rappaport and Sprague,[9,10] they include, besides a multiplicity of practical features, means for recording simultaneously the total vibratory spectrum in three distinct frequency responses. These include the well-known linear, stethoscopic, and logarithmic response.

In their approach to the problem of frequency response of the system, these authors started by elucidating the principles governing the operation of a damped diaphragm and investigating the acoustic properties involved in the average stethoscope. They then proceeded to study the frequency response characteristic of both the interchangeable chest pieces and the tubing, including the ear pieces. After a quantitative evaluation of the linear distortion introduced by the average acoustic stethoscope in the transmission of the vibrations to the human ear, they designed and built an amplifier and a transducer incorporating an acoustic filter. The frequency response of this system literally simulated the characteristics of the average stethoscope. This they labeled *stethoscopic response*. Then, after studying the further modification of intensity introduced by the logarithmic response of the

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This study was made during the tenure (A. A. L.) of a teaching grant of the National Heart Institute, U.S.P.H.S.

† The data pertaining to some of the existing apparatus are not made available. The main reason seems to be industrial competition.

TABLE I

Comparison of Systems Used by Various Workers in Phonocardiography

Range	Mannheimer[12]	Maass and Weber[18] (Holldack[35])	Leatham[13,14]	Rappaport and Sprague[10]	Butterworth[34]	Zalter and Luisada[67]	Rosa and Luisada[71,72]	Luisada and Magri,[31] Johnston and Overy,[29] Eddleman[26]
Ultra-low	—	—	—	Linear (0–∞)	—	—	0.01–5 (Nominal = 0.01)	(0–∞)
Low	5–25 (Nominal = 12)	—	—	—	—	5–25 (Nominal = 4)	5–25 (Nominal = 5)	—
Low-Medium	12.5–50 (Nominal = 4)	35 (t) (Slope 7.5/octave)	Low (cut-off at 120 slope = 8 db/octave)	—	Filter = low (Nominal = 60)	30–60 (Nominal = 30)	—	—
Medium-low	25–100	70 (m1)	—	—	Filter = 1/4 rotation (Nominal = 80)	60–220 (Nominal = 60)	—	—
Medium	50–200 (Nominal = 100)	140 (m9) (Slope 24/octave)	Middle (cut-off at 300 slope = 11 db/octave)	Stethoscopic (Nominal freq. = 200 slope = 12 db/octave)	Filter = 1/2 rotation (Nominal = 110)	120–240 (Nominal = 120)	—	—
(Auscultatory)	h	140 (m2) (Slope 18 db/octave)	High (cut-off at 500 slope = 15 db/octave)	Logarithmic (Nominal freq. = 200 slope = 18 db/octave)	—	—	—	—
Medium-high	100–400 (Nominal = 200)	250 (h1) (Slope 24 db/octave)	—	—	Filter = 3/4 rotation (Nominal = 250)	240–480 (Nominal = 240)	—	—
High	200–800 (Nominal = 400)	400 (h2) (Slope 24 db/octave)	—	—	Filter = full rotation (Nominal = 800)	480–960 (Nominal = 480)	—	—
Characteristics	High-pass filter (24 db/octave)	Rated frequency = −20 db below normal or 10% of maximum	Different slopes	Different slopes	High-pass filter slope = −14 db/octave; low-pass filter = +10 db/octave	Band-pass filter (−18, −24, −30, −36)	—	—
		Different slopes					Band-pass filter (− 24)	Linear response (0–∞)

The symbols used in this table are conventional letters used by the various authors.

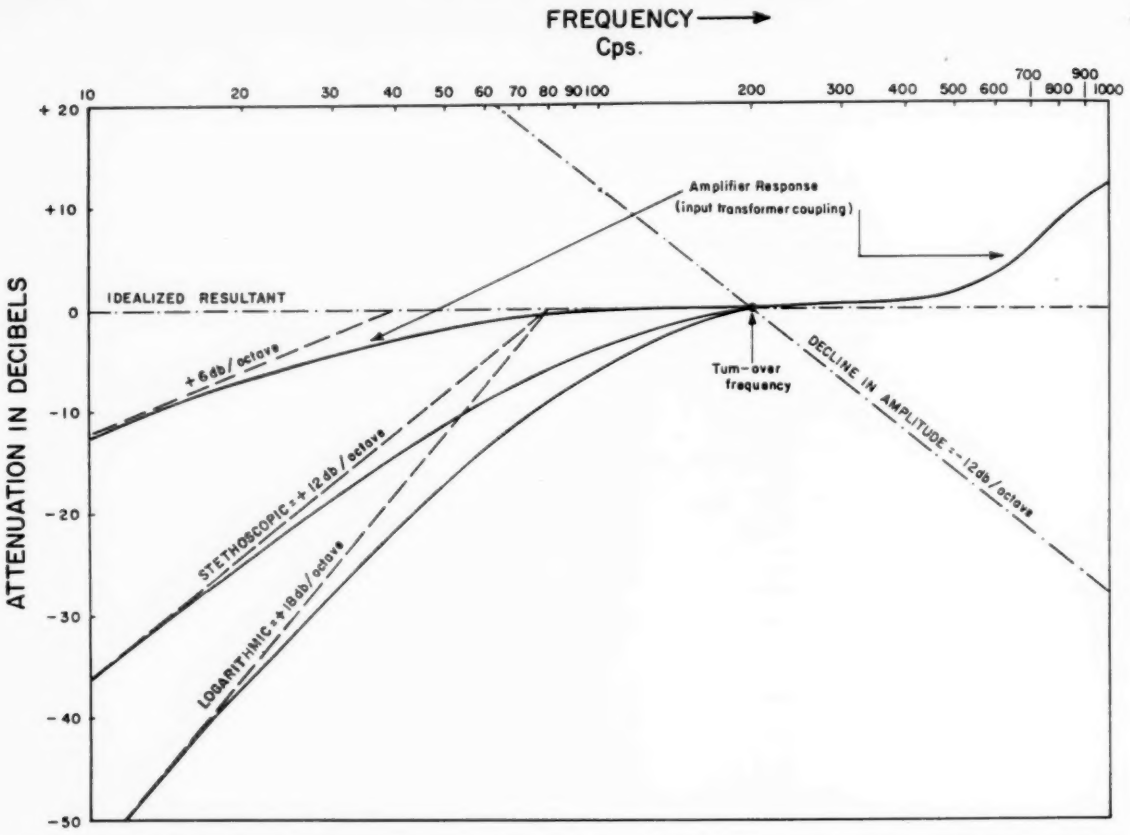

FIG. 1. The Twin-Beam frequency response-characteristics. (Based on data and graph supplied by M. B. Rappaport.[10])

human ear, they further introduced into their amplifier circuit an additional electrical filtering circuit which rendered the final record a graphic picture of the vibratory spectrum as perceived by the human ear, after distortion by the stethoscope. This they labeled *logarithmic response.* Viewed from this angle, and taking into account the above objective, they succeeded in reproducing the effect with fair accuracy. However, when the frequency response of the total system (including the transducer, the amplifier, and the galvanometer) is critically appraised as to the frequency correction to which the vibratory spectrum has been subjected, the resultant response does not appear to be the optimal method for either the registration or the study of the spectrum of sounds.

Basically, this system obtains an equalizer-like effect, with low-frequency attenuation below 200 cps and high-frequency lift above 200 cps (made possible through the input transformer coupling of a dynamic microphone) (Fig. 1). The resultant tracing can be roughly evaluated as an attempt to equalize or reduce to a uniform level the amplitudes of the different components of the vibratory spectrum. This has the decided advantage of simultaneously recording the frequency components of the total spectrum.

The stethoscopic response was obtained in the twin beam through the use of a dynamic microphone which has a response equal to a rise of 6 db/octave with increase in frequency, and a very nearly flat response of the amplifier.[60] The logarithmic response was obtained through introduction of a filter circuit which creates a frequency respnnse corresponding to that of the ear (response equal to a rise of 12 db/octave with increase in frequency).

DISADVANTAGES

Acoustically, of course, using an audiophone or a loudspeaker, the amplified sounds perceived by the average human ear duplicate the sounds as perceived through a stethoscope. However, *from a graphic point of view, the tracing is not satisfactory.* This is mainly the result of substituting

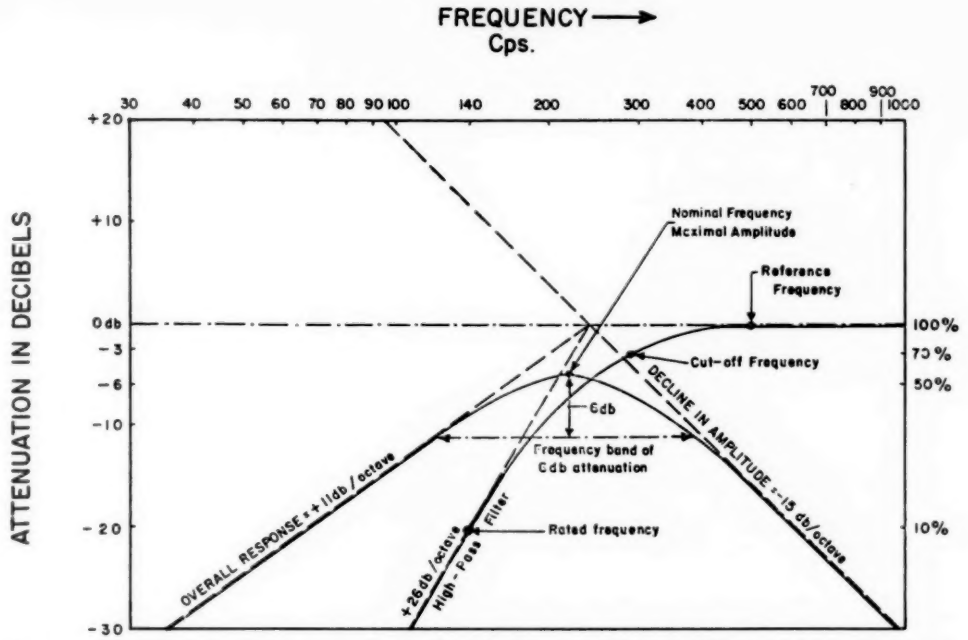

FIG. 2. Frequency response characteristic using 26 db/octave high-pass filter at the rated frequency of 140 cps. (Adapted and modified from Maass.[18])

a visual pattern for the analytic and synthetic powers of audition. The information derived from a stethoscopic tracing cannot be considered the equivalent of auscultation.[5,19,50] Graphically the stethoscopic response presents a picture with predominance of the low-frequency vibrations including a high portion of the infrasonic and subliminal bands. This may be difficult to interpret, at times, because the frequency and position in the spectrum of the individual vibrations cannot be determined. Furthermore, the simultaneous registration of such a relatively wide band precludes a clear demarcation between sounds and/or murmurs which might otherwise be audible. Finally, critical murmurs, even though recorded in proportion to their intensity level, may appear insignificant in the stethoscopic tracing and only slightly more pronounced in the logarithmic tracing (in the presence of high-pitched vibrations). Often the amplitude is insufficient for clear-cut differentiation from the ambient noise which renders interpretation sometimes difficult.[58]

DRAWBACKS IN CLINICAL USEFULNESS

In spite of several desirable characteristics of this system, high-pitched murmurs, like those of aortic insufficiency, are often poorly recorded[51,52] thus decreasing the usefulness of phonocardiography in a delicate field, where auscultation (with its selective properties and psychologically enhanced amplification) often still proved superior.

The diastolic extra sounds and the low-frequency murmurs, like the diastolic rumble of mitral stenosis, are only fairly well recorded by this system.[51,52] As this happens in questionable cases of mitral stenosis, this drawback undermines the clinical usefulness of the system.

SCHWARTZER PHONOCARDIOGRAPH

The F. Schwartzer Company of Germany has developed a phonocardiographic system incorporating several novel features. The frequency response of this system is partly based on the suggestions of Maass and Weber[18,35] in their study of differentiating filters. In this system (originally introduced by the Elema Company of Sweden, whose phonocardiograph will be described later), three novel modes of approach were adopted as being best suited to the study of vibratory phenomena:

(1) Graphically, the vibratory spectrum lends itself to better visual scanning if split into adjacent and overlapping frequency bands, which are then amplified and recorded.

(2) The octave system, empirically chosen for these bands, seems to be the best for the purpose.

(3) These results can be accomplished by the

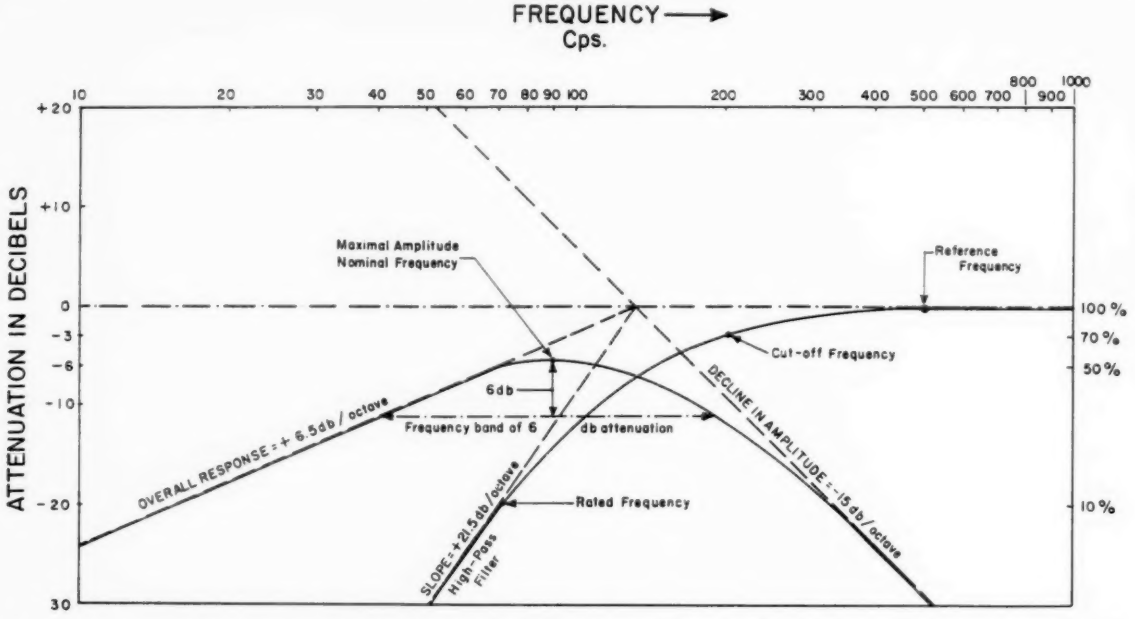

FIG. 3. Frequency response characteristic using 21.5 db/octave high-pass filter at the rated frequency of 70 cps (Adapted and modified from Maass.[18])

insertion, at specified frequencies, of high-pass filters into the system, thus dispensing with the (otherwise necessary) band-pass filters. This is made possible by the fact that the natural decline in amplitude of the frequency spectrum with increase in frequency compensates for the lack of an additional low-pass filter, which might be otherwise necessary (Fig. 2).

The insertion of a high-pass filter involves certain problems of particular importance in phonocardiography, since the critical area of attenuation is obtained in conjunction with the upper curved part of the filter transmission curve. To circumvent any vagueness that might arise as to the exact definition of any point along the curve, Maass suggested adopting a point of reference, say 500 cps, the transmission of which can be regarded as 100 per cent of input (its attenuation would then be zero db). The point of 10 per cent transmission (20 db attenuation) can be regarded as the rated frequency of a given filter characteristic. Below the rated frequency, the slope of the filter (which is linear on a logarithmic scale) determines the rate attenuation in decibels per octave. The resulting over-all response of the system can be seen in Figures 2 and 3, which show two filters, with a rated frequency of 140 and 70 cps and a slope of +26 db/octave and +21.5 db/octave, respectively, introduced into the circuit. The frequency of maximal amplitude (nominal frequency)* does not correspond with the rated frequency and is somewhat above it.

The frequency band of 6 db attenuation, so delimited, includes the frequency of maximal amplitude plus those frequencies above and below it whose amplitude is 6 db less (50 per cent of maximal). For a rated frequency of 140 cps and a slope of +26 db/octave, this band extends from 120 to 360 cps. The width of the band is, of course, a function of the attenuation specified. By grossly spacing the rated frequency at octave intervals of 35, 70, 140, 250, and 400 cps, and keeping the slope constant at 24 db/octave (except for the lowermost rated frequencies of 35 and 70 cps, which have a slope of 7.5 db/octave and 18 db/octave, respectively) the spectrum is divided in adjacent and partly overlapping bands, which are then amplified to a similar graphic amplitude by providing an amplification ratio of 1:4 for each octave. This ratio is supposed to compensate for the decreasing magnitude which occurs with increasing frequency. Thus, through the exclusive use of high-pass filters, strategically placed at octave intervals, the spectrum is split into bands suitable for amplification and recording. However, in choosing

* The nominal frequency corresponds to a point on the filter curve whose slope is equal but not opposite in sign to the slope of the vibratory spectrum.

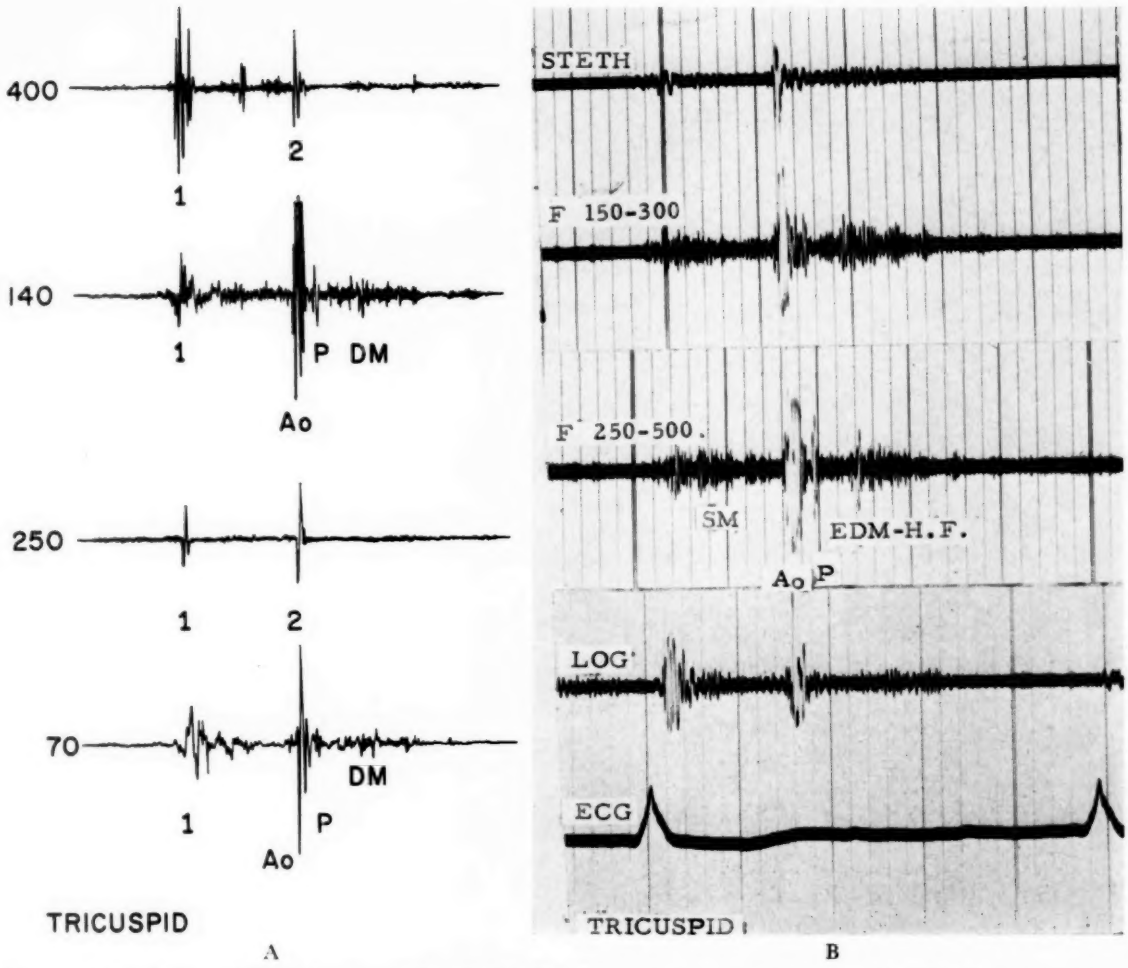

FIG. 4. The phonocardiogram in a case of aortic insufficiency over the same area taken with the Schwartzer system (A) and the modified stethoscopic system (B).

the rated frequency as the frequency of reference for any one band, an element of confusion was injected concerning the frequency of maximal amplitude (or nominal frequency) of the band in question. At the lower end of the spectrum, where high-pass filters of 18 db/octave and 7.5 db/octave slope are used, respectively, the resultant frequency bands are of different dimension as compared to the higher frequency bands (Fig. 4). This may be justified from a graphic standpoint, but is undesirable for comparative purposes.

DISADVANTAGES

The system used by the Schwarzer Company has several other features which may not be ideal:

(1) The microphone is very heavy; its weight renders it unhandy and may even introduce an element of error by stretching the skin (selective attenuation of lower frequencies through formation of a diaphragm). This has been made necessary by the use of a direct-contact (button) crystal microphone.

(2) The use of curves having an envelope for the registration of higher frequencies is necessary if a direct-recording system is to be used. Obviously such a system cannot be used for frequency analysis, as only the duration, intensity, and variation of intensity are recorded. Finally, at higher frequencies, the direct-contact button becomes critical and is likely to introduce extraneous vibration with the slightest motion.

ELEMA PHONOCARDIOGRAPH

The Elema Company of Sweden can be

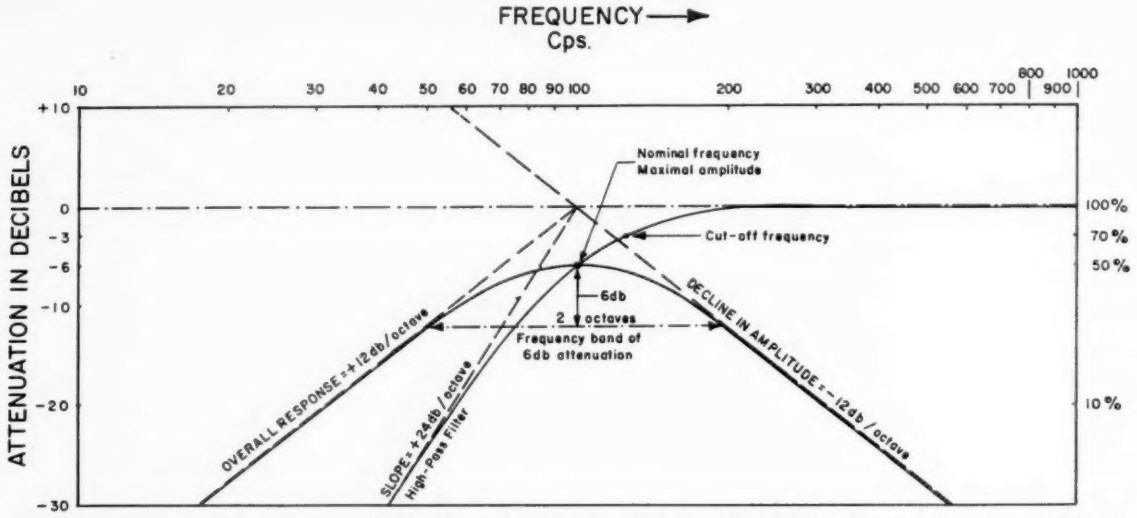

FIG. 5. Frequency response characteristic using a 24 db/octave high-pass filter with a nominal frequency of 100 cps (Adapted from Mannheimer, based on personal communication.)

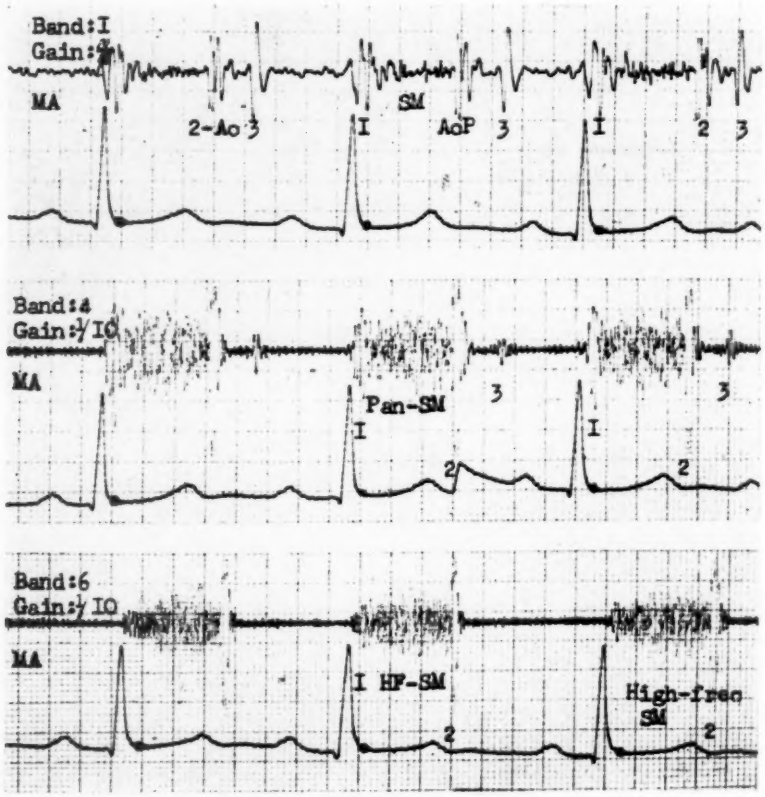

FIG. 6. A case of mitral insufficiency using the Elema Mingo graph. At nominal frequencies of 12, 100, and 400 cps.

credited for creating a system of phonocardiography which incorporated band-pass filters based on the original work of Mannheimer.[11,12] In 1948, a simplified apparatus was introduced with only RC-coupled high-pass filters.[61] This was made possible, as mentioned earlier, by the steep decrease in amplitude of the sound vibrations with rising frequency. The Elema uses an

air-coupled velocity microphone (dynamic) having a sensitivity rise of 6 db/octave, together with complementary RC filters. In this way, a high-pass filter effect of 24 db/octave was obtained through the additive effect of the microphone-amplifier combination.

By appropriate design, the frequency spectrum is divided into six adjacent bands of similar dimensions. The nominal frequency (or frequency of maximal amplitude) of the band in question was adopted as the frequency of reference of that band. This is in accordance with the proposals put forth by the Committee on Standardization of Phonocardiography in 1956, which stipulated that "The channels employed should be named with the frequency at which the slope of the increase of sensitivity, by increasing frequency, is 15 db per octave." At such nominal frequency (in this case 12 db/octave), the oscillations are recorded with the largest amplitude. Above and below the "nominal frequency," the band of 6 db attenuation (or 50 per cent decrease) extends over a space of 2 octaves. As is evident from Figure 5, the nominal frequency is the central frequency, as well as the frequency of maximal amplitude. Frequencies above or below the band in question undergo sharp attenuation at the rate of 12 db/octave, a fact which results in a symmetrical pattern for the band in question (Fig. 6). In accordance with the above scheme, the nominal frequencies of the bands were spaced at octave intervals, i.e. at 12, 25, 50, 100, 200, and 400 cps.

Summary

The characteristics of several existing American and European phonocardiographs are discussed. Their desirable features and shortcomings are analyzed.

(*References for this article appear at the end of Part III, p. 38*)

Phonocardiography

III. Design of the Ideal Phonocardiograph*

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IN THE PREVIOUS two notes, the various requirements of an ideal phono system were first discussed. Then, the characteristics of several existing systems were analyzed and their advantages and disadvantages presented. It is now time to see whether a more ideal and still flexible apparatus can be built.

IDEAL DESIGN

In the design of a phonocardiographic system, the pertinent principles and the possible methods discussed in the first and second part of this study should be further evaluated if the empiric approach in design is to be substituted by a rational one. Considering the multiplicity of factors involved, we had to weigh a priori the rationale behind every alternative before deciding in favor of either solution.[67]

Having sketched in broad outline the desirable response characteristics of the various parts of a phonocardiographic system, we proceeded, within the practical limitations of available components, to assemble, test, modify, and match the various parts into a coherent whole.

A system so constructed may not prove optimal on performance. However, on the basis of our former experiences, we felt that this would offer a firmer foundation, theoretically free from gross errors, and would be amenable to improvements and modifications if necessary. On the other hand, the empiric method of testing a number of filters with various slopes and cut-off frequencies, now being tried in Europe,[56] is likely to yield more information as to the optimal system to be adopted, even though theoretical considerations would obviate the need for detailed testing.

Following is a brief evaluation of the pertinent factors considered in our design of a phonocardiograph.

Equalized Response of Total Spectrum vs. Adjoining Frequency Bands: In considering the optimal method for a thorough scanning of the vibratory spectrum, the system of dividing the spectrum into adjoining bands appears to be the most promising. As pointed out earlier, this stems from the basic dissimilarity between the optical and the acoustic mode of observation.

Both the stethoscopic and the logarithmic methods give a more or less equalized response. Therefore, the various bands of vibrations are so modified in amplitude as to become of equivalent value. While the auditory system can still appreciate certain bands of frequencies within the spectrum (through selective psychologic emphasis),[33] the visual system cannot do the same thing in observing a graphic tracing. On the other hand, a selectively filtered band of frequencies will stand out and reveal the outstanding features of sounds and murmurs.

In selecting the band system, it is necessary to stress those dimensions of the sound phenomenon that lend themselves more accurately to a graphic and optical evaluation. These are an intensity relationship of vibrations and frequency characteristics.

Octave System vs. Linear System: The system of dividing the frequency spectrum in bands, each comprising an octave, is better suited for the study of the vibratory phenomenon.[37] This is true, first, because the ratio of energy below nominal frequency to that above nominal frequency over a symmetrical band is closer to unity with the octave system as compared to the linear system; and second, because a linear system with equal bands would require too many bands

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This study was made during the tenure (A. A. L.) of a teaching grant of the National Heart Institute, U.S.P.H.S.

to scan the whole spectrum, and the bands in the high-frequency region would contain very little extra information in relation to each other.

Overlapping vs. Contiguous Bands: A certain amount of overlap is desirable for the following reasons: (1) For a murmur extending over a limited range, the possibility of its being missed, should it fall between adjacent bands, is minimized. (2) Sharper transition may be achieved in order to emphasize individual frequency components while keeping others small. However, the overlapping should be moderate and symmetrical. For example, one fourth at each side might be allowed to overlap. This would still leave 50 per cent of each band free of overlapping and is different from the wide and irregular amount of overlapping which existed in Mannheimer's original system.[11]

Band Width, Band Symmetry, Frequency of Reference, Attenuation over One Band: In an octave system, a band width of one octave appears to be the logical choice. This would involve a duplication of results in the upper frequency region, which is nevertheless beneficial in certain cases. However, the operator should have the possibility of moving a larger band including two octaves in the higher frequency region, thus avoiding unnecessary repetition of tracings. The *frequency of reference* of the band in question should then correspond with *the nominal frequency* or *frequency of maximal amplitude.*[55] Furthermore, if the nominal frequency occupies a central position, the band in question should be symmetrically deployed with respect to the nominal frequency. Finally, in order to obtain a flat frequency response over a band of one octave, the upper and lower limiting frequencies of the band in question can be allowed an attenuation of not more than 3 db, or 70 per cent of the amplitude of the nominal or mid-frequency.*

Beyond the limits of the octave band, the degree of attenuation is steeper and depends on the degree of transition desired.

INSTRUMENTATION FACTORS

In trying to adhere to the above-mentioned response characteristics, an attempt was made to eliminate all variables from the various stages and to concentrate what modifications are envisaged into the filter stage. Such an approach necessitated an equipment (transducer-amplifier-galvanometer) having the most perfectly linear characteristics possible (i.e., the response should be flat with no distortion over the range of the vibratory spectrum). Such a system allows maximum flexibility in the manipulation of the final response characteristics. Our choice in each instance was influenced by the following considerations.

The Transducer

The choice of a transducer for phonocardiographic practice is an exacting procedure.[48,49,59] Beginning with the crude carbon-granule microphone of Einthoven,[7] many authors have applied themselves to the task of adopting and modifying microphones of different characteristics to suit the specific application in phonocardiography.[9,11,16,21,26,29,59] Basically, however, microphones can either transduce *displacement* (crystal and capacitor microphones) or *velocity* (electrodynamic and electromagnetic), depending upon the type used.[22] None of the currently used types has an absolute advantage or superiority; their merits are only relative and are partly the result of the peculiarity of the phenomenon under study. For a vibratory spectrum sloping in amplitude at some 15 db/octave, the high-frequency vibrations are at a great disadvantage because of their extremely small amplitude. Even for vibrations of equal intensity, the high-frequency components are still smaller in amplitude in view of the natural decline of 6 db/octave. It is apparent that the use of a displacement microphone, irrespective of its performance characteristics, would favor graphically the low-frequency elements, even though the final picture is an exact replica of the various amplitudes as they appear at the surface of the chest wall.

A velocity microphone, on the other hand, tends to emphasize (i.e., relatively amplify) the high-frequency elements, in the sense that two vibrations of unequal amplitude but similar intensity would be equally registered through greater emphasis given to the high-frequency in comparison with the low-frequency vibrations.[22,29] Apart from these basic principles, a multiplicity of factors should be considered in the selection of a microphone. Beranek[37] presents an exhaustive list designed to help the experimenter in selecting a microphone. Of the pertinent factors related to this problem, the nature of the sound field, the range of sound pressure level, and the frequency range under study are of primary importance.

Nature of the Sound Field: Of necessity, considering the intensity level of the vibratory phenomenon, free-field transmission is ruled out. Instead, the mode of transducing can be either *direct* (through a connecting rod or button) or *indirect* (by interposing a closed air chamber be-

* This value is derived from electronic consideration, since it corresponds to the half-power frequency. From acoustic consideration, it also corresponds to the point where the ear can detect those lowered gains, since they are 70 per cent of maximum.

tween the surface of the chest wall and the diaphragm of the microphone).

The direct method was adopted by several authors for use in phonocardiography in conjunction with electromagnetic and crystal microphones. The main feature of such a device lies in the chest piece, which is designed with a view to eliminate extraneous noises as may originate from the instability of the button. This is accomplished by providing either a double-walled suction funnel surrounding the button or a ring of sponge rubber in a grooved heavy casing.

In the indirect method, the shape, volume, and dimensions of the closed chamber are critical factors in the design because of the associated cavity resonance that tends to distort the response of the microphone at the resonant frequencies.[19] A lucid discussion on the principles governing the operation of a damped diaphragm, together with the frequency characteristics of various chest pieces, can be found in a paper by Rappaport and Sprague;[9,10] suffice it to say that, if the volume of a cylindrical cavity is kept large enough (around 10 cu cm), with a ratio of diameter to height of 3:1, the response characteristics remain linear up to the resonance point, which is well above the upper frequency range of the sound spectrum (1,000 cps).

Dynamic Range: The dynamic range of the microphone should be wide enough to encompass the dynamic range of the vibratory phenomenon. As the amplitude over two decades (10–1,000 cps) can be in the ratio of 10,000 : 1, covering a dynamic range of 80 db, the microphone should be capable of handling or transducing with equal fidelity those components at the extreme ends of the spectrum.[45,46] At the lowermost intensity level (i.e., upper frequency range of the spectrum), the amplitude may be as low as 0.01–0.001 dyne/sq cm. For the microphone to transduce such a weak signal into a suitable voltage for amplification, either the sensitivity (voltage produced per unit pressure) should be high or the noise level should be low, because the sensitivity of a microphone is nothing else but the complement of its own noise.

Laboratory microphones are usually calibrated in terms of their open-circuit voltage for a given sound pressure in a free field.[37] For phonocardiographic use, *the open-circuit pressure response is better suited for calibration*, since it simulates the condition under which the microphone is used.[12,19] It differs from the *free-field response* in that the sound pressure is measured at the diaphragm of the microphone rather than in a free field. The results are expressed in terms of open-circuit voltage for a constant sound pressure uniformly distributed over the diaphragm. For a reference voltage of 1 volt and a reference pressure of 1 dyne/sq cm, the response in *decibels* is $20 \log e/p$, where e is the open circuit voltage and p is the pressure at the diaphragm. Stated differently, at the reference level of 0 db, a pressure of 1 microbar applied at the diaphragm of a hypothetical microphone generates a voltage output of 1 μv. The actual output, however, falls short of 1 v for the same applied pressure. Thus, for a microphone whose output level is -55 db, the voltage generated is 55 db below the reference level of 0 db (1 v dyne/sq cm). Obviously, the smaller the number of decibels, the higher the output level of the microphone, and the more sensitive this is.

The limiting factor in the dynamic range at low-intensity levels is the *thermal noise voltage* generated in the microphone. This "noise" is created by the thermal agitation of molecules in the resistive components of the microphone, that of air molecules in contact with its diaphragm, or both. The voltage thus produced is an inherent characteristic of every microphone, though its level may vary according to the design and type of microphone. For a given microphone, the noise represented by voltage output can be expressed in terms of the equivalent sound pressure, which theoretically it might generate in an ideally silent microphone.

This equivalent noise-sound pressure can be compared to the threshold of human hearing, because a signal below this level cannot be usefully transduced by the microphone, as it would be masked or submerged in the noise voltage inherent in the output of the microphone. A signal to be usefully transduced should be at least 20 to 30 db above this threshold level of self-noise in order to stand clearly above the base line. It is evident that, at low-intensity levels, the useful output of a sensitive microphone with a high noise level cannot be greater than that of a proportionally less sensitive microphone having a lower noise level.

Comparison of the threshold pressure for the human ear and for a given microphone should prove to be a good index of their respective sensitivities. Thus the self-noise generated by a well-designed coil microphone over a band of three decades (10–10,000 cps) can be roughly equated to a sound pressure level of 10 to 20 db above the threshold pressure of the human ear

(0.0002 dyne/sq cm). If we consider that the magnitude of the signal should be at least 20 db above the noise level, the threshold pressure which a coil microphone can efficiently transduce is 40 db higher than the threshold pressure of the human ear. In contradistinction to the human ear, the sensitivity of the microphone is *linear* over a wide band, while the sensitivity of the ear is a function of the frequency. Nevertheless, in the high-frequency range the ear is just as sensitive as, or more than, a well-designed coil microphone.

The Frequency Range: The frequency response characteristic of most microphones is linear over the major part of the frequency spectrum of the human heart.[21,48] A calibration curve of the microphone indicates the open-circuit voltage that is produced as a function of the frequency for a constant sound pressure.[19,21,68,69] The constant sound pressure generally used in conjunction with calibration is 1 dyne/sq cm.[55] Except for specially designed circuits, the frequency response at the lower end of the spectrum is nonlinear in most microphones. Thus, frequency distortion in this region is inevitable, though it may not be apparent as the magnitude of the signal is such as to compensate for the decrease in sensitivity. However, for accurate design, the rate of attenuation should be specified in the calibration curve of the microphone. Once the above-mentioned specifications are met, the choice of the proper microphone for the purpose at hand narrows itself to the degree of desired precision in measurement, or, more precisely, to the degree of tolerated distortion.

Linear Distortion—Frequency Distortion: The degree of linear distortion tolerated in phonocardiographic work should be reduced to a minimum. The frequency response, as stated earlier, should be linear over the frequency range under study within the limitation of design, thus eliminating the tendency to suppress or accentuate certain frequencies. This is particularly important, since the fidelity with which a complex signal of transient character (such as heart sound) is reproduced is a function both of the frequency response characteristics and of the phase shift in relation to frequency.

Phase Distortion: This type of distortion assumes a greater importance in the low-frequency region of the spectrum (1–40 cps), where the shape and configuration of the periodic waveform is of diagnostic importance. In the high-frequency region (above 100 cps) a certain amount of phase distortion can be tolerated without visually affecting the final configuration of the transient sound under study. A delay not in excess of 20 milliseconds at 100 cps in relation to the delay at 1,000 cps cannot be considered excessive from a graphic point of view, though acoustically it may have a bearing on the perceived character of the sound in question.

The Amplifier

For phonocardiographic work, voltage amplification alone can be considered sufficient for the operation of the system, since virtually no power or energy is consumed in driving the final transcription stage. As the range of frequencies involved falls mainly within the audio range, an RC-coupled, two-stage or three-stage audiofrequency amplifier, with a midband of sufficient width to cover the frequency range of the vibratory spectrum, is considered satisfactory. The fundamental frequency of the complex waveform comprising the apex cardiogram is roughly in the vicinity of 1 cps. A low cut-off frequency (0.1 cps) and a high cut-off (2,000 cps) can, therefore, be considered wide enough for the signal at hand. Within this band, the frequency response should be linear throughout and only 3 db lower at the cut-off frequencies. Nonlinear distortion and phase distortion should likewise be reduced to a minimum and quantitatively specified. This is particularly important in the low-frequency band, where the configuration of the complex wave, everything else being constant, is a function of the distortion incurred in passing through the transducer-amplifier system.

The amount of gain or amplification required in conjunction with phonocardiographic practice can be estimated from the dynamic curve of the vibrations, provided the sensitivity of the microphone and the intensity of the signal for every frequency are known. Thus, if the signal amplitude at 100 cps can be considered as unity, the amplification needed to bring up the signal at 1,000 cps to the same level would be about 40 db, since the spectrum decreases in amplitude over the same range by a similar amount. More important than absolute amplification is the *signal-to-noise ratio* in the final tracing. For a ratio of 100:1 in the tracing, the signal at the input should be 40 db above the noise level of the transducer. For a ratio of 5:1, which gives a poor resolution at best, a signal of 14 db above the noise level is needed. This limitation needs

consideration in the selection of a transducer amplifier system.

The Filter

The use of acoustic filtering in phonocardiography, though functional and economical, cannot be considered ideal because the degree and extent of attenuation is a function of several factors which cannot be accurately controlled. High-pass electrical filters are now universally used. The use of band-pass filters, however, seems to have been abandoned in favor of the high-pass filters, since similar results can be obtained by the latter's use alone. Band-pass filters were originally studied by several authors,[5,11] but the use to which they were put proved to be of limited clinical value. As early as 1926, Williams and Dodge[63] used a system incorporating a band-pass filter as an auscultatory wave analyzer, with fairly good results. However, the clinical use of such a system for auscultatory analysis can hardly be justified on biophysical grounds. Mannheimer,[11] employing band-pass filters together with a calibrated system, used the apparatus for the study of the absolute-intensity level of frequency components in the vibratory spectrum. There can be little doubt that a graphic mode of analysis is the method of choice in conjunction with a wave analyzer incorporating a band-pass filter.

In our opinion, the substitution of a single high-pass filter,[51–53] though practicable, cannot be considered sufficiently accurate. Furthermore, since the noise level of the system, and ultimately its resolution power, is a function of the band width, the inclusion of a band-pass filter becomes less a matter of cost or preference than of necessity. A variable electronic band-pass filter, consisting of RC elements, the gain of which is unity in the pass band but drops outside the pass band at a specified rate, is the unit of choice. Such a filter provides maximum flexibility of adjustment of both *the frequency of the band center* and *the width of the band*. Ideally, the possible frequency range of the pass band should be wide enough to accommodate the frequency spectrum under study. The distortion introduced should not exceed 1 per cent of the output signal, while the internally generated hum and noise should not exceed 100 μv. Peaking circuits, when included, help to eliminate any confusion in the setting of the cut-off frequency at any desired range.

The Galvanometer

All galvanometers, regardless of design, have definite limitations in sensitivity and frequency.[70] In the selection of a galvanometer for a specific application, it is necessary to weigh the relative importance of each of four main characteristics: frequency response, sensitivity, phase angle, and damping. A galvanometer so selected as to obtain a desired characteristic must, of necessity, be a compromise of all the aforementioned characteristics. Following is a brief discussion of pertinent factors.

Frequency Response: In order to supply galvanometers which will perform over a wide frequency range, yet be relatively flat, most galvanometers are so designed that, when damped to 64.5 per cent of critical damping, they will have a flat response within ± 5 per cent of the final response up to 60 per cent of their undamped natural frequency. Fluid-damped galvanometers will vary from the above response because of the dynamic action of the fluid. These will have a frequency response of from 30 to 50 per cent of their undamped natural frequency.

Current Sensitivity: Maximum current sensitivity is always associated with maximum resistance and minimum natural frequency. Should it be desirable to utilize a galvanometer with higher natural frequency, it must then be remembered that a lower sensitivity will be the result of the accompanying higher sensitivity.

Damping: Two methods of damping are normally used: (1) Electromagnetic damping for galvanometers having a relatively low natural frequency, usually less than 500 cps. (2) Fluid damping for galvanometers having a higher natural frequency.

When using galvanometers that require electromagnetic damping, it is very important that the correct damping resistance or input impedance be used in order to insure the specific flat frequency response. In the case of fluid-damped galvanometers, the input impedance will have very little effect on the frequency response.

From the above considerations it becomes evident that phonocardiographic technique represents one of the most exacting applications in this field. This is readily inferred if the dynamic range of the vibratory phenomena and the frequency spectrum under consideration are to be matched to a galvanometer of sufficient sensitivity and flat frequency response to meet the above requirement. *In the low-frequency range*, where the intensity of the signal is high enough and the sensitivity of the galvanometer is adequate, a galvanometer having a natural frequency of 500 to 600 cps should prove satisfactory (in the sense of large deflection per unit current) to cover the frequency range of the vibratory spectrum.

New Systems

MODIFIED STETHOSCOPIC SYSTEM

The inadequacy of the stethoscopic response (and for that matter, the logarithmic in conjunction with a diaphragm chest piece) to give a graphic definition of a given sound or murmur is readily apparent to the worker in the field.

Unless a perfectly straight base line is secured, a murmur of low intensity may be difficult to appreciate and, as such, it can hardly be differentiated from minimal irregularity of the base line induced by artefacts or ambient noise. It is evident that, unless the signal-to-noise ratio is increased, erroneous conclusions are likely to be made. Further amplification cannot improve the resolution power, since the relative amplitude of the different vibrations is preserved unchanged. Our early attempt to circumvent the limitations imposed by the characteristics of the stethoscopic response was in the nature of improvisation. However, though simple in concept, it proved to be of practical value in resolving and clarifying problematic tracings. The necessary modification was carried out by the simple introduction of a variable band-pass filter into the system. This was made possible by the fact that the stethoscopic response can be considered as an equalized form of the total vibratory spectrum with equal emphasis on both high- and low-frequency components. Such an output, when fed into a variable band-pass filter, can be split into any number of pass bands of different widths and cut-off frequencies. The output of the filter can then be amplified, if necessary, and finally applied to a galvanometer circuit for recording.

A variable band-pass filter with high- and low cut-off frequencies, independently tuned, continuous from 20 to 2000 kc, was used for this purpose.* A 24 db/octave slope for each side was thought to be optimal. The noise level was comparatively high, though still less than 5 mv. Since the filter input is stethoscopic in characteristic, the filtered output for a particular band is simultaneously recorded. The tracings in Figures 1 to 6 are examples of the selective amplification over a specific band. The visual representation of the same phenomenon through two systems of filtration can be roughly compared as to their relative merits. From practical considerations, and judging by the improved resolution and better definition of the resultant tracing, such a modification proved to be advantageous both for the detection and accurate registration of murmurs and sounds, as well as for the purpose of frequency analysis.[51–53] Nevertheless, this modified system suffers from several shortcomings: (1) The frequency response characteristic for any pass band is not exactly linear, since the stethoscopic response cannot be considered perfectly linear over the total spectrum. (2) The inclusion of a reference tracing (when using a twin-beam) is not possible. (3) The procedure is time-consuming and somewhat complicated.

* Manufactured by Krohn-Hite Corporation, Cambridge, Mass.

INTEGRATED PHONO CHANNEL

In order to incorporate the desirable features of an integrated system into a single unit, two separate phono channels were designed following our specification,* as a part of a larger multichannel unit.[64,66]

In addition to the stethoscopic response characteristic (120–500 cps, with high-pass filter of 12 db/octave attenuation) and ECG response characteristic (0.1–200 cps), a built-in band-pass filter circuit was included. The filter circuit included two graduated dials for varying, respectively, the high and low cut-off frequencies in octave steps. The lowest cut-off frequency was set at 25 cps and the highest at 2,500 cps. At cut-off, the attenuation slope of the filter-amplifier is rated at 18 db/octave both for the high- and the low-pass. A crystal microphone with a linear response between 20 and 8,000 cps is used. The output of the channel is applied to the vertical plates of a cathode-ray tube for recording, and simultaneously, to a monitoring oscilloscope.

Such a compact arrangement is a distinct advantage, as it offers a maximum of flexibility of operation and choice of response characteristic for any purpose. The frequency range of the vibratory spectrum (1–1,000 cps) is more than covered by the frequency response of the amplifier-filter system (0.1–2,500 cps). Evidently, for the registration of the low-frequency vibrations (linear phonocardiogram), the time constant of the crystal microphone has to be of the order of several seconds; this can be done by a switching arrangement in the same microphone or by using a microphone of different RC time constant for any one purpose.

* We wish to thank Mr. L. Scheiner, Chief Engineer of Electronics for Medicine, Inc., White Plains, N. Y., for his kind collaboration.

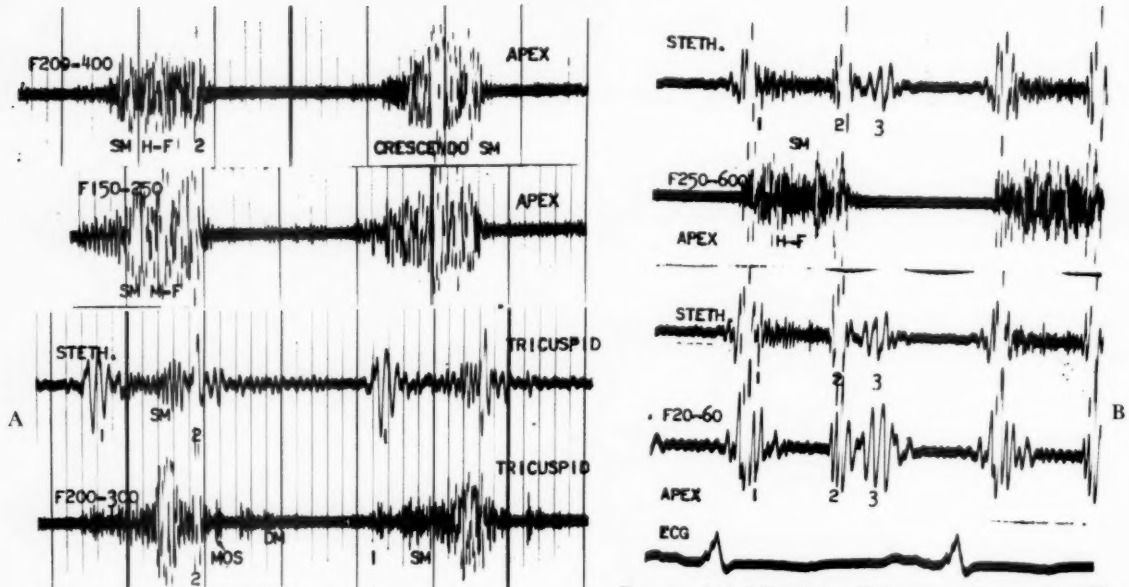

FIG. 1. (A) Mitral insufficiency and stenosis. The crescendo type of systolic murmur is revealed best by the frequency range 150–250 cps while the low-grade diastolic rumble is shown best by the stethoscopic tracing. The opening snap (MOS) is especially evident in the 200–300 cps range. (B) Mitral insufficiency. There is an all-systolic murmur revealed by the 250–600 cps frequency range which appears as decrescendo in the stethoscopic tracing. The latter shows well a third sound, but this is even better revealed by the 20–60 cps range (change of amplitude, phase, and pattern with frequency).

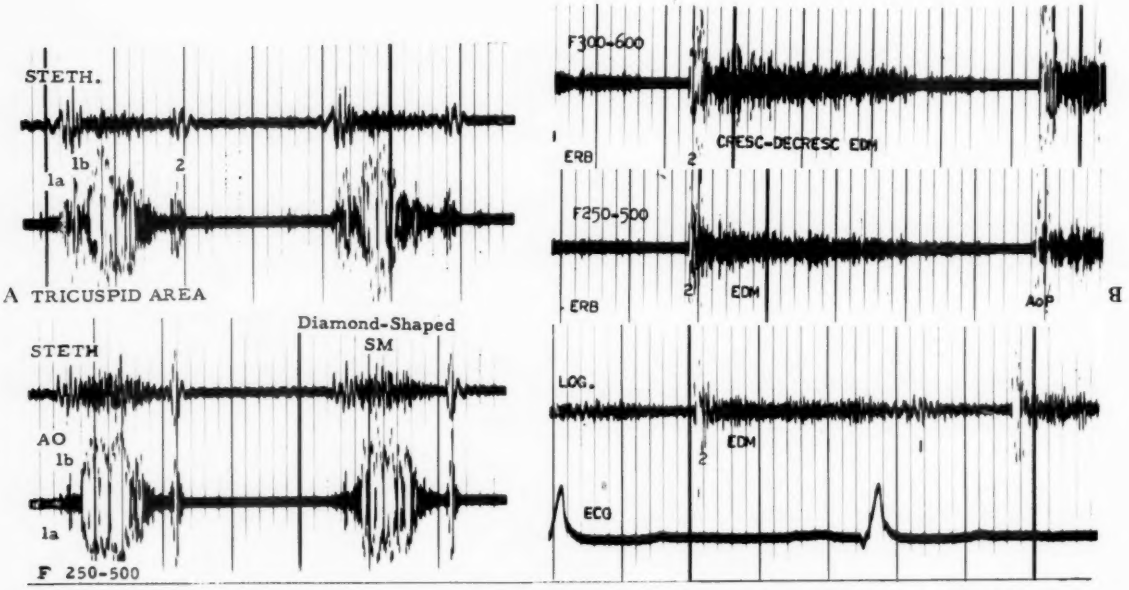

FIG. 2. (A) Aortic stenosis. The diamond-shaped systolic murmur is revealed best or only by the 250–500 cps range which also shows the two components of the first sound (1*a* and 1*b*) and the details of the second sound (change of pattern with frequency). (B) Aortic insufficiency. The long diastolic murmur is best revealed by the 300–600 cps range where the vibrations acquire a crescendo-decrescendo configuration (change of pattern with frequency).

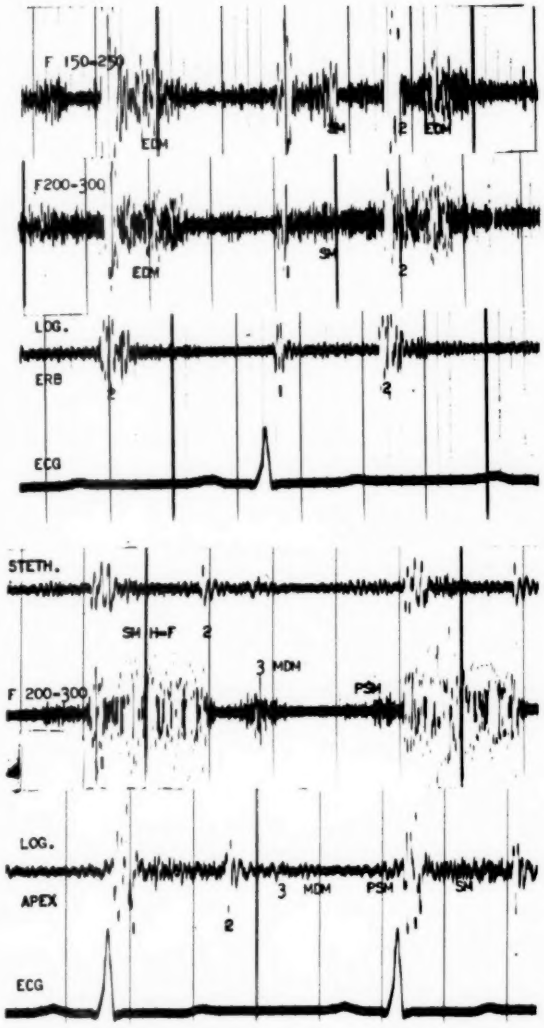

FIG. 3. Combined mitral and aortic insufficiency. The top three tracings, recorded at Erb's point, show how the diastolic murmur (EDM) assumes a different configuration with change of frequency. The lower three tracings, recorded at the apex, reveal the tremendous change in amplitude and configuration of the systolic apical murmur (SM) which seemed of secondary importance when recorded by stethoscopic or logarithmic methods.

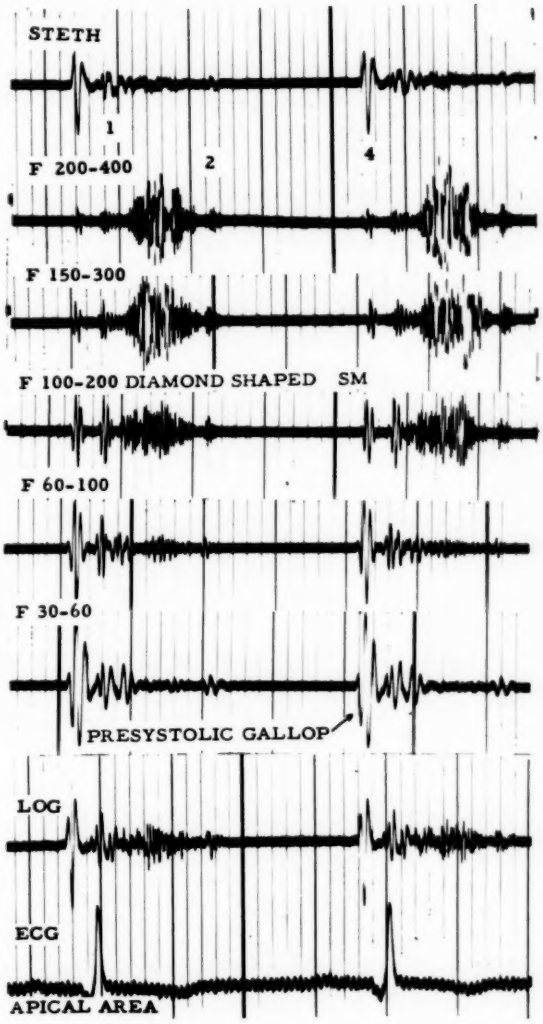

FIG. 4. Myocardial infarction, one day after the attack. There is a large fourth sound (presystolic gallop), best revealed by the 30–60 cps range. There also is a systolic murmur which is diamond-shaped and is best revealed by the 150–300 cps range (change in configuration, amplitude, and pattern with change in frequency).

A record so obtained is a function of the amplifier-filter, since both the crystal microphone and the cathode-ray tube can be considered as perfect linear devices. The unit proved extremely satisfactory in the low-frequency range (up to 200 cps). At the higher frequencies, however, the quality of the tracing was blurred because of the inherent difficulty associated with the application of the cathode-ray tube to multiple recordings. In this case, the electronic switching arrangement is used to operate at least four separate channels or beams.* At low frequency, the switching frequency is high enough to produce a continuous record. At high frequency the tracing appears interrupted (i.e., dotted) and, therefore, somewhat blurred and not clearly defined. Moreover, a pass band with 18 db/octave attenuation cannot be considered ideal, as it is not symmetrically displayed around the nominal frequency. It became increasingly apparent that, if a system is to incorporate those

* A recent modification permits operating only two channels, thus improving the definition of the tracing.

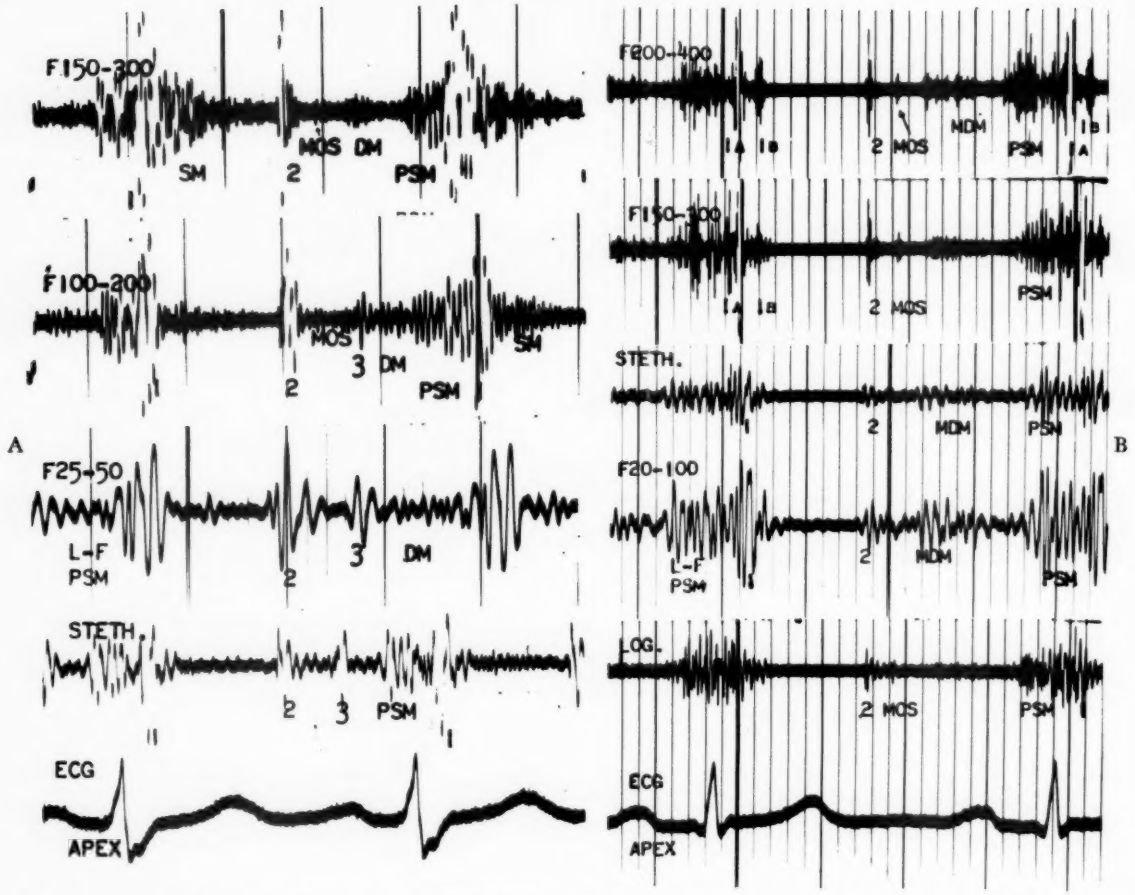

FIG. 5. (A) Mitral stenosis with minimal insufficiency. The presystolic murmur (PSM) is revealed best by the 100–200 cps range; the systolic murmur (SM) in decrescendo is visible only in the 150–300 cps range; the third sound is shown by the stethoscopic and by the 25–50 cps and 100–200 cps ranges (changes in amplitude, pattern, and definition revealed by the various frequency bands). (B) Pure mitral stenosis. The frequency range 200–400 cps reveals very clearly the components of the first sound, the opening snap (MOS), and the presystolic murmur. The latter assumes a crescendo-decrescendo pattern (see second cycle) (changes in amplitude, pattern, and definition in different frequency bands).

frequency characteristics elucidated earlier in this paper, the optimal way, though least economical, is to assemble and match units of known frequency response, distortion, and noise level. An example of tracings obtained with this system is presented in Figure 6A.

A NEW PHONO SYSTEM

A new phono system has been built in this laboratory.* It consists of a condenser microphone, a preamplifier, a variable band-pass filter, another amplifier, and a set of galvanometers with different frequency responses.

* This was made possible by the warm collaboration of Mr. J. Hilliard, Director of Advanced Engineering, Altec-Lansing Corp., Beverly Hills, Calif., and Mr. J. Pesek, Field Engineer of Altec Service Co., Chicago, Ill.

Microphone: The capacitor or condenser microphone was first adapted to phonocardiography by Trendelenburg. It was used by McKusick[41,42] in conjunction with the spectral analyzer. Greatbatch[47] used the same microphone together with a Noye filter for the study of transients above 1,000 cps. Groom[59] made use of the capacitance principles, employing a modified capacity microphone developed by the General Motors Laboratories for the accurate study of the complex waveform. In fact, the condenser microphone represents one of the first precise acoustical instruments available, and is still extensively used in fundamental acoustic measurements because of its ideal flat frequency response characteristics and its low minimal distortion.

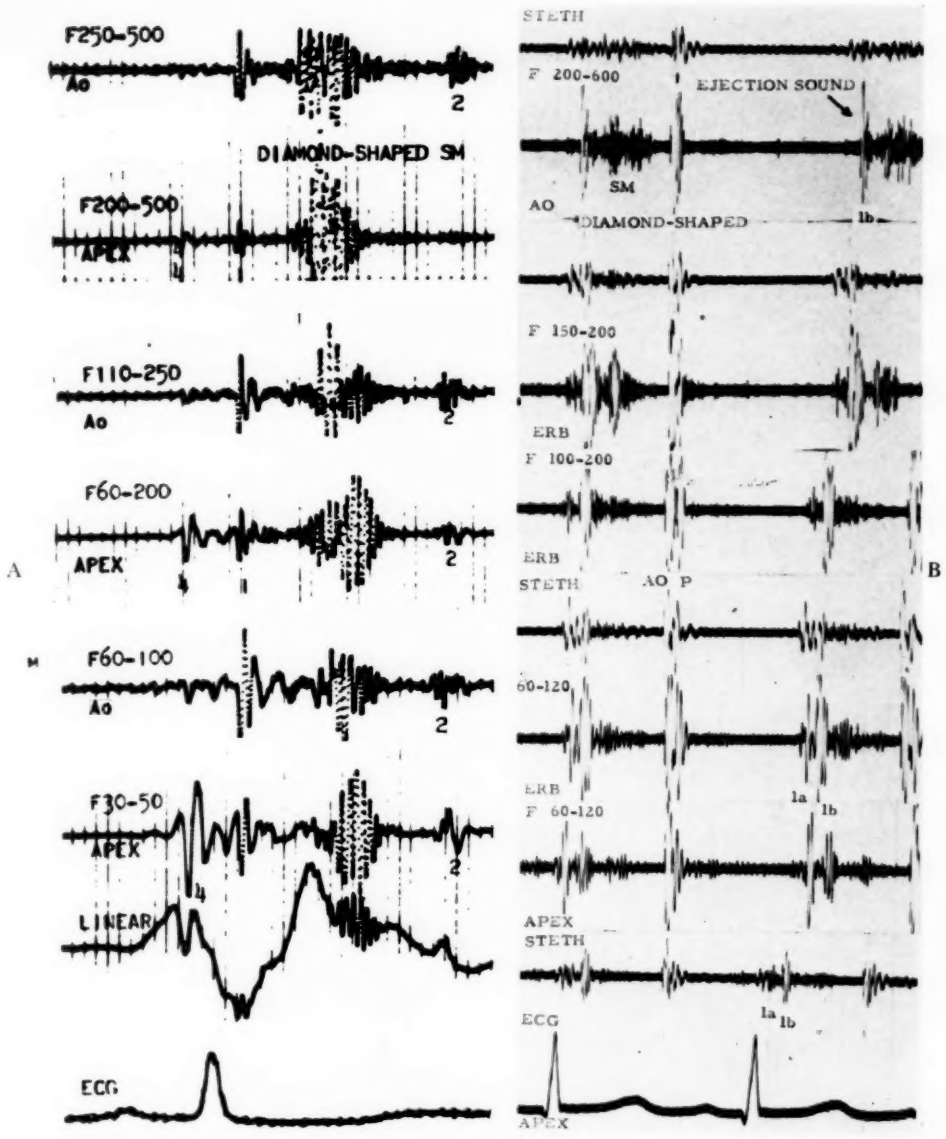

FIG. 6. Aortic stenosis and minimal insufficiency. (A) A midsystolic group of vibrations assumes a diamond-shaped form in the 200–500 cps range. The fourth sound is revealed best by the 30–50 cps range and becomes minimal in the 200–500 cps range (these tracings were taken with the "integrated" phono channel with cathode-ray oscillograph). (B) Clearly individualized components of the first sound (1*a* and 1*b*) in the 60–120 cps range; the second component, however, becomes even larger and better defined in the 200–600 cps range. Splitting of the second sound is apparent in the 100–200 cps range (changes in amplitude and definition in the various frequency ranges).

Altec-Lansing is supplying a group of condenser microphones which are capable of measuring a wide frequency and intensity range. Of these, three types can be adapted for use in cardiovascular research. Originally the medical microphone system consisted of a 21 BR-150 microphone. Like all other condenser microphones, this is a pressure-operated transducer. The response of this microphone is said to be flat down to 30 cps, and 5 db down at 10 cps. This microphone was rendered adaptable to auscultation by coupling it to a Bowles stethoscope head (combined with bell-diaphragm chest piece). Such a modification defeats by its nature the purpose for which a microphone with linear characteristics is sought, since the vibrations are

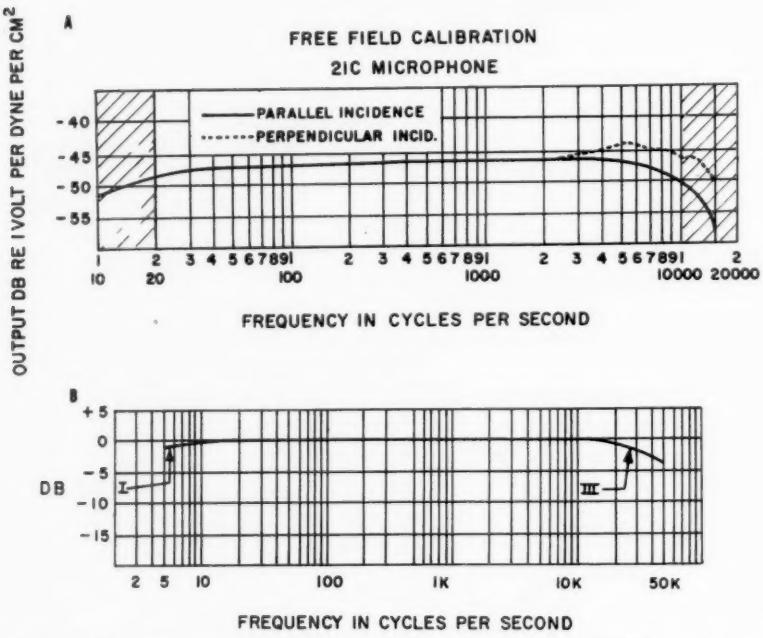

FIG. 7. (A) Frequency response characteristic and output level of condenser microphone 21-D. (B) Frequency response of preamplifier 442-B.

subjected to the distortion and resonance associated with the chest piece.

The 21-MA and its predecessor the 21-M have been modified to 21 RB-150 and 21-D, respectively, for direct use on the chest. In both, a rubber-molded piece is interposed between a microphone diaphragm and the surface of the skin. Thus, the microphone has two diaphragms—one is in the standard position which forms the vibrating plate of the capacitor; the other, separated from the first by an air space, forms the direct contact for the transmission of vibrations. The air space adds an acoustic high-pass filter for the attenuation of those static pressure variations which may result from the application and handling of the microphone. This microphone-chest piece combination is said to introduce some 20 db attenuation of ambient noise.[62] In our experience, the 21-MA microphone proved fair in the frequency range of up to 200 cps. Nevertheless, the inclusion of the high-pass acoustic filter in the infrasonic range tends to accentuate the nonlinearity of the microphone in that range and thus increase the distortion of the low-frequency components. *Above 200 cps, the microphone proved unsatisfactory.* The introduction of the molded rubber diaphragm piece reduces sensitivity of the microphone by 20 db.

This reduction of sensitivity in the frequency range where the signal intensity is at best minimal has proved critical because further amplification can only be obtained at the expense of high signal-to-noise ratio. The 21-D microphone is similar to the 21 RB-150, though slightly more sensitive.* Its frequency characteristic and output level can be seen in Figure 7*A*. The microphone is 1.5 cm in diameter; when coupled to the subminiature tube used as a cathode follower, the total assembly becomes a cylindrical unit of 1.5 cm in diameter and 8 cm in length. The problem of adapting the cylindrical microphone assembly weighing less than 75 Gm to a suitable chest piece involved the design and tooling of several end pieces. The purpose of such an end piece is fourfold: (1) to secure a stable hold for the microphone (holding the microphone hanging from its connecting cord is an inconvenient improvisation at best); (2) to provide an airtight chamber for the exclusion of extraneous vibration and attenuation of ambient noise; (3) to obtain better transmission of vibrational energy to the microphone diaphragm through the airtight chamber; and (4) to reduce to a minimum any distortion which may be introduced through the end-piece resonance properties.

These requirements were best satisfied by se-

* −47 db re 1 volt dyne/sq cm for the 21-D vs. −56 db re 1 volt dyne/sq cm for the 21 BR-150.

curing the microphone assembly through a tight-fitting plastic cylinder which mushroomed at the applied end into a conical enclosure of 4 cm in diameter and 1.8 cm in depth. To avoid the application of pressure (e.g., rubber straps) a grooved rim with suction attachment was added. This proved ideal for securing the microphone on the skin without undue pressure on its surface other than that induced by the vibrational energy (Fig. 8).

Amplifiers: The output of the microphone system is fed into a low-noise precision-gain voltage preamplifier, the 442-B.* The 442-B is a newly designed amplifier intended for instrumentation application where low noise output is of prime importance. This is a three-stage, 40 db voltage amplifier with high negative feedback and low distortion. The frequency response can be seen in Figure 7*B*. The output noise at 40 db is 0.001 v. An input attenuator provides four steps of 10 db per step. An additional plug-in transformer allows the input of a dynamic microphone to be matched to that of the amplifier input impedance (100,000 ohms). The output of the amplifier's cathode follower is intended to drive loads in excess of 10,000 ohms.

Filter: A variable electronic band-pass filter of high input impedance with unity gain in the pass band is connected to the above amplifier. The 330-A† was chosen for this purpose because it offers independently adjustable high and low cut-off frequencies from 0.02 to 2,000 cps with an attenuation rate of 24 db per octave outside the pass band. A peaking value slightly greater than 0.6 reduces the attenuation at the corner frequencies by approximately 9 db and permits the selection of the band width of one octave. The cut-off frequency is therefore identical with the setting of the dial, both for the low and high cut-off. The internally generated hum and noise is rated at 100 μv in the low-amplitude position. The distortion introduced by the filter does not exceed 0.5 per cent of the output signal. Such output characteristics are considered satisfactory and allow for a high signal-to-noise ratio. Nevertheless, in the low input amplitude position, the filter could handle only 20 db gain; further amplification resulted in overloading when using the capacitor microphone. The magnitude of this signal, after 40 db amplification for normal heart sounds, was found to vary between 5 and 7 v. Such a signal is far above the capacity of the filter to handle (1 v) without overloading. Using the filter in the "high" input amplitude position (10 v) resulted in a significant drop in the output signal intensity and a parallel decrease in the signal-to-noise ratio. In the frequency range up to 200 cps, an amplification of 0 to 20 db proved adequate for recording with a galvanometer of sufficiently high natural frequency. This is to be expected, since the major portion of the vibratory energy is to be found in this range above 200 cps (i.e., setting the low cut-off frequency of the high-pass filter at 200 cps). Overloading of the filter proved the limiting factor in the critical range, where 40–80 db amplification is needed for complete scanning of the vibratory spectrum. It should be mentioned that changing of the sequence of the set-up by putting the filter ahead of the amplifier resulted in a higher signal-to-noise ratio.

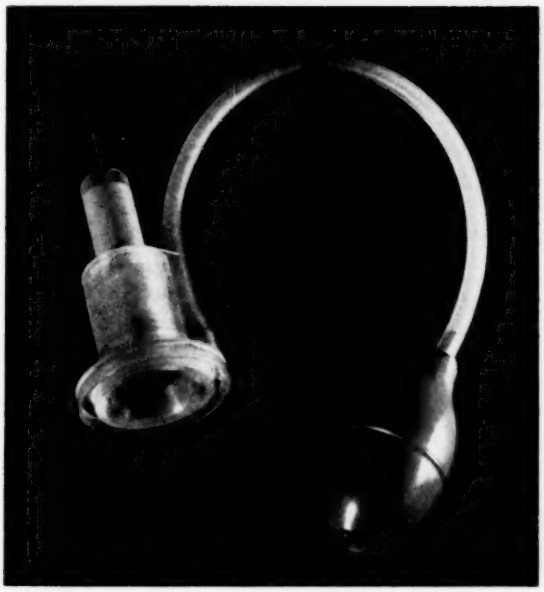

FIG. 8. The microphone chest piece.

Second Amplifier—Additional Filter: The problem was circumvented in two ways: (1) A second amplifier (similar to the above described 442-B) was connected to the output of the filter, allowing a total maximum amplification of 80 db. (2) An additional L-C filter was applied at the output of the first amplifier, attenuating the energy-laden frequencies below 200 cps. With these additional devices, the output of the microphone can be amplified by the full 40 db and applied to the filter input without fear of overloading. Thus, the two amplifiers, respectively

* Designed and manufactured by the Altec-Lansing Corporation, Beverly Hills, Calif.

† Manufactured by the Krohn-Hite Corporation, of Cambridge, Mass.

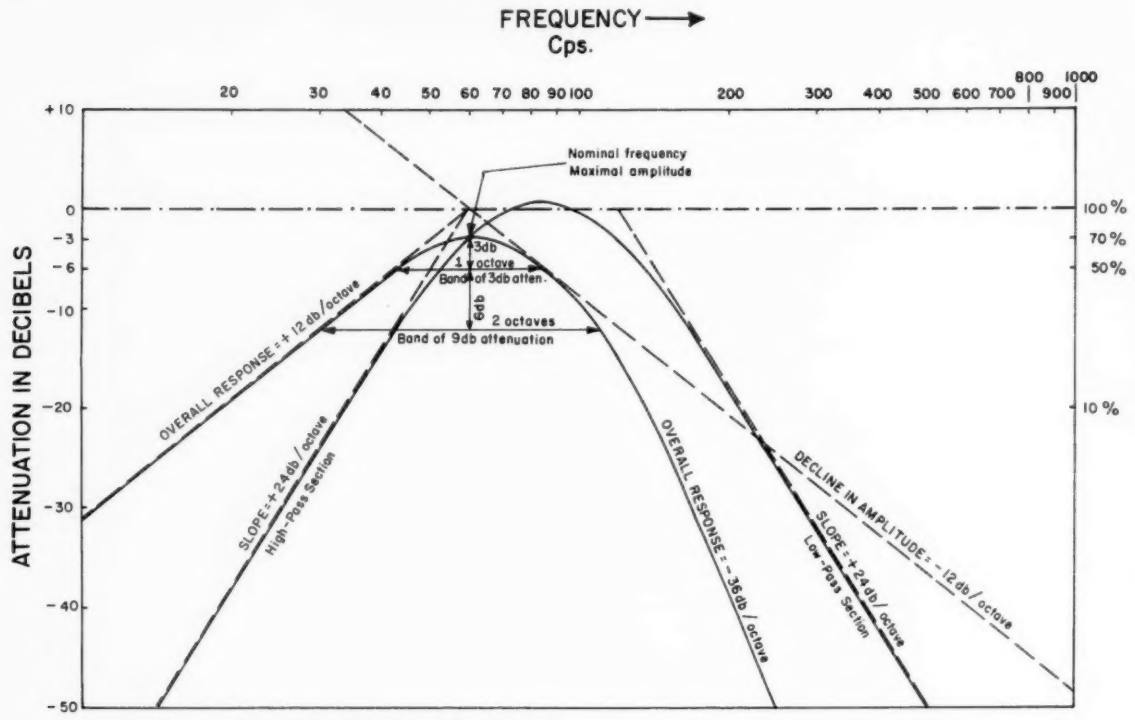

FIG. 9. The frequency response characteristic of the new phonocardiographic system.

placed before and after the filter jointly yield a full 80 db amplification.

The use of a calibrated microphone, together with a precision gain amplifier (specified in decibels) and the unity gain filter, has the great advantage of being a *calibrated system.* Given the degree of amplification, both the relative and the absolute intensity of a given signal can be computed.

Recorder: A multichannel recorder* incorporating a magnet-block assembly for 6 plug-in pencil-type galvanometers is used. A monitoring scope can be plugged into any channel for simultaneous observation. Galvanometers of different frequency responses, sensitivities, and damping characteristics are used in order to ascertain the natural frequency best suited for a given frequency band. Galvanometers of undamped natural frequency of 250–3,000 cps were tried. As we have consistently attempted to secure a flat frequency response in the operative frequency range, it is evident that only the specified ratio of the natural frequency response can be used to advantage.

The BB 3,000, intended primarily for recording transients above 1,000 cps, proved sensitive for high-frequency vibrations but with high amplification. The BB 1,100, with a flat frequency response of up to 700 cps can be considered satisfactory for all practical purposes. The BB-650, proved satisfactory in the range 120 to 400 cps, which is the band having a balance between sensitivity, on the one hand, and moderate frequency range, on the other.

Using the above-mentioned system, we have proceeded to scan the vibratory spectrum, as delineated earlier, in bands of one octave. By simply setting the dials at octave intervals, any fundamental octave band can be chosen. The decimal system is the easiest to handle. However, because of the natural distribution of normal and pathologic frequencies we feel that an octave system of 15, 30, 60, 120, 240, 480, 960 is better suited for scanning. In our system, as can be seen from Figure 9, the low cut-off frequency is actually the nominal frequency about which the band of one octave is symmetrically displayed. Furthermore, a band of 3 db attenuation can be considered flat over the same range and is therefore ideal. The bands of one octave do not overlap and are therefore continuous. It is obvious that for complete scanning of the spectrum from 15 to 960 cps a total of six bands is necessary. On the other hand, over

* Manufactured by New Electronics Products, Ltd., London, England.

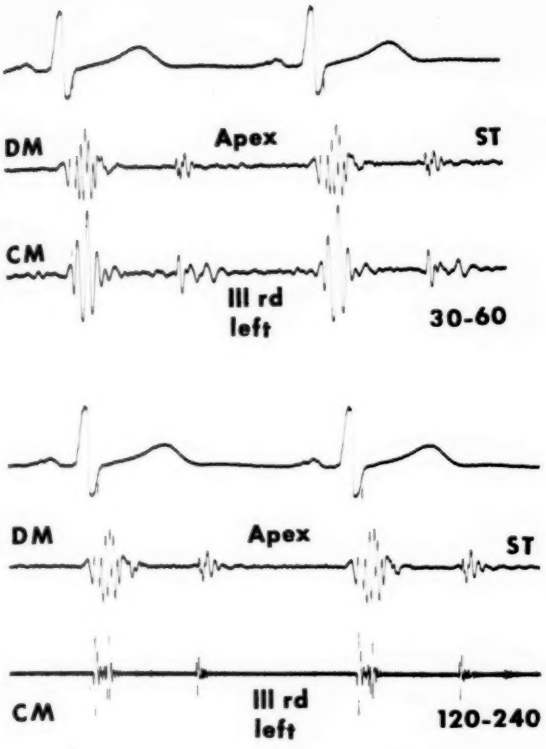

FIG. 10. Phonocardiograms of a normal subject of age 17 recorded with the new phonocardiographic system. *DM*, dynamic microphone; *CM*, capacitor microphone; *ST*, stethoscopic response.

a band of two octaves (9 db attenuation), 50 per cent overlap is obtained on each side. Such a system, as we plan to demonstrate in subsequent studies, offers a degree of flexibility and accuracy unobtainable otherwise. The authors feel that this new system will greatly contribute to the practical usefulness as well as the theoretical systematization of phonocardiography through its correctly standardized response and flexibility. Figures 10 and 11 demonstrate tracings obtained with the new phono system.

SUMMARY

(1) The main components of a phonocardiographic system are discussed, with the aim of selecting the most desirable characteristics for the construction of a new system.

(2) Various methods of scanning the vibratory spectrum are discussed.

(3) Three new phonocardiographic systems are presented. One consists of a modified "stethoscopic" system; one is an integrated phono channel, using an oscillographic cathode-ray recorder; the third is a newly constructed

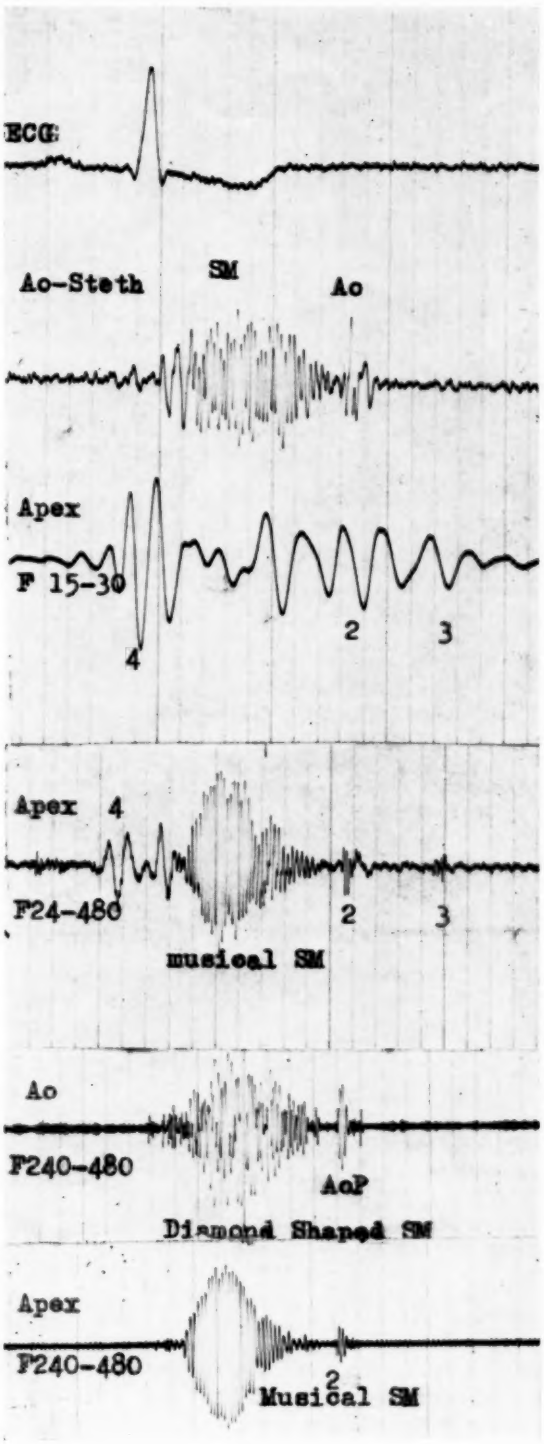

FIG. 11. Phonocardiograms in case of aortic stenosis recorded with the new system. Large fourth sound, high-pitched, musical systolic aortic murmur, split second sound.

apparatus, based on previously discussed principles.

(4) Tracings recorded with these systems are presented, and their merits are underlined.

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Notation of Phonocardiographic Waves

Suggestions for an International Method

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IN THE PAST, phonocardiograms recorded in various countries have been marked with different symbols which represented the abbreviations of words in different languages. This has caused a certain difficulty in evaluation of tracings by scientists of other countries.

While the physical characteristics of the apparatus should be marked on each tracing according to a recently proposed international agreement, it is to be hoped that researchers of various countries will also adopt a unified system of notation which may considerably further the usefulness of phonocardiography.

As will be easily seen, all the notations are taken from Latin words with the exception of snap (K) and friction rubs (FF), for which a conventional letter has been selected.

PHONOCARDIOGRAM

"Phonocardiogram" originates from Greek words meaning "sound-heart-graph." The abbreviation of the term will be *PCG*.

HEART SOUNDS OR TONES

There is no disagreement on the fact that four heart sounds may be recorded even in normal subjects. These should be marked with the Arabic numerals 1, 2, 3, 4.

The *1st sound* is occasionally divided into two groups of vibrations. The latter will be marked as 1′ and 1″. The reason for this purely descriptive and not interpretive notation is that there is still some disagreement about the mechanism of production of the various vibrations. If the 1st sound is composed of four or five large vibrations, the latter should *not* be marked, for the time being, even though a definite interpretation for their meaning has been suggested with the possibility of a clear-cut notation.*

The *2nd sound*, which is marked by the number 2, is often divided into two groups of vibrations. There is general agreement that, both in normal subjects and in most clinical cases, the first group corresponds to closure of the aortic valve and the second group to closure of the pulmonic valve (an exception is represented by rare cases of "paradoxical splitting"). Therefore, the two groups of vibrations will be marked as 2A and 2P. If a paradoxical splitting occurs, an inversion of this symbol would be appropriate (2P and 2A).

The most common *diastolic sounds* are the 3rd or 4th, or both. These sounds may be unduly increased in intensity in clinical cases, causing the so-called triple and quadruple rhythms (gallop rhythms). As the latter represent merely an accentuation of the former (with possible changes of frequency), both the normal and pathologic *3rd* and *4th sounds* will be marked as 3 and 4.

In the rare cases where there is a *double 3rd* or *double 4th sound*, they will be marked as 3′ and 3″ and 4′ and 4″. If there is a summation type of triple rhythm, this will be marked as 3-4.

SNAPS AND CLICKS

Snaps and clicks will be marked with the letter K. The *opening snap* of the mitral valve will be called KD (diastolic snap), as it is practically the only diastolic click or snap which can be observed.

Systolic snaps or *clicks* will be marked as KS, whatever the phase of systole in which they fall. The so-called ejection sound of the aortic or pulmonary artery can also be marked KS, unless one is convinced that this snap correresponds to the second group of vibrations of the

* The author suggested the letters MTPA for the four vibrations composing the 1st sound which he considered connected with four valvular events.

1st sound, in which case it would be marked as 1″.

Murmurs

Murmurs may occur in either systole or diastole. *Systolic murmurs* will be called SSS, while *diastolic murmurs* will be called DDD.

In order to be able to mark not only the phase of a murmur but also its shape (diamond-shaped, decrescendo, crescendo), it is suggested to use small and capital letters and to put a small "o" wherever the murmur is absent or indistinct. The following are the resulting notations:

Systolic murmur in decrescendo	= Sso or Sss
All systolic murmur	= SSS
Systolic murmur in crescendo	= sSS or ooS or osS
Diamond-shaped systolic murmur	= sSs
Early diastolic murmur in decrescendo	= Ddd or Ddo or Doo
Early diastolic murmur which is diamond-shaped	= oDo or oDd
Presystolic murmur	= odD or ooD
Continuous murmur	= sSDd
Friction rubs	= FF, whether in systole or diastole

Frequency and Amplitude

No notation is contemplated for the time being for these two variables of the sound vibrations. It is obvious that the degree of amplification and the type of filter greatly affect these variables. The suggestions adopted at the Third World Congress of Cardiology will be of help in the consideration of the frequency range of a murmur. Notation of the degree of amplification should await further work on calibration.

Location

In regard to the place where a phonocardiogram is taken, a certain agreement has been already reached following suggestions by Duchosal. The data can be simplified as follows: One should note the intercostal space, site right (D) or left (S), and the number of centimeters from the marginal line of the sternum. Examples: 2D5, 2S3, 4S5.

Reports on Pericarditis

Studies in Pericarditis

I. Differentiation of the Acute Idiopathic Form from That Occurring in Disseminated Lupus*

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The etiologic mystery surrounding the syndrome labeled "acute idiopathic pericarditis" remains unsolved despite the intensive efforts of physicians recruited from many medical disciplines. The virologist, rheumatologist, phthisiologist, and others continue to track each clue which might lead to the erasure of the word "idiopathic" from the title applied to this disorder.

As evidence from all sources has accumulated, considerable doubt has arisen that all cases of acute idiopathic pericarditis (AIP) will ultimately be placed under a single etiologic heading. There is a growing suspicion that a variety of etiologic agents may be capable of producing the clinical pattern now recognized as AIP. It now appears that the syndrome currently carrying the designation "AIP" will ultimately be reorganized into subgroups, each of which will have a different etiologic origin, but quite similar symptoms.

There are currently three such etiologic subgroups which have achieved some degree of recognition. Perhaps the least support is granted to the theory that abortive infection by specific bacterial or fungal agents may be incriminated in AIP. A larger and growing faction suggests that viral agents are the causative factors in many instances of this syndrome. The third and perhaps largest segment of physicians believe that it is some form of "allergic" phenomenon which reaches clinical expression in the form of AIP.

Recently, particular interest has been directed toward the last-named ("hypersensitivity") theory by the recognition of an ever-increasing array of clinical syndromes which seem related to the development of "allergic states" to both endogenous and exogenous agents. In this group, we may place the so-called allergic vasculitides, the postcommissurotomy syndrome, the postmyocardial infarction syndrome, and the overlapping entities loosely united under the term "collagen vascular diseases."

Our interest in the "allergic" theory of AIP causation has recently been heightened by experience with several cases of disseminated lupus erythematosus (DLE) which presented as instances of AIP. Study of these cases suggested to us that one of the ultimate "fragments" of the entity now called AIP may consist of the group of individuals with DLE who are currently being given the diagnostic label of AIP.

Therefore, an effort has been made (1) to determine whether such diagnostic confusion is a clinical reality and, if it is, how frequent such confusion may be; (2) to indicate those *parallel features* of these two disease states which may lead one into diagnostic error; and finally, (3) to define those divergent features by which AIP and DLE may readily be separated.

It is felt that such an analysis will serve to alert physicians to the possible masquerade of DLE as AIP. In addition, the material presented will make plain the treacherous conse-

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quences of accepting AIP as a valid diagnosis rather than as a symbol of ignorance demanding careful investigation.

Plan of Study

To answer the questions posed above, the following groups were selected for study.

Group A: The case records of 23 patients with "classical" acute idiopathic pericarditis seen at this hospital from January, 1954, through March, 1957, were analyzed in detail. Cases were accepted when (1) a clinical history of significant substernal or precordial chest pain, a pericardial friction rub, and "classical" evidence of pericarditis by electrocardiogram—or any two of these in combination—had (2) occurred in a patient in whom all known etiologic agents had been excluded to the satisfaction of the attending staff at the time of discharge. This group is referred to hereafter as our *AIP group.*

Group B: The case records of 14 patients with DLE seen during the same period, *in whom pericarditis was present at the time of admission* by the criteria outlined above, were also analyzed. The diagnosis of DLE was ultimately established in 12 patients by positive "LE tests" or post-mortem examination, and in 2 patients by overwhelming clinical and laboratory evidence supporting this diagnosis. This group is referred to hereafter as our *DLEP group.*

Group C: The literature relating to AIP was extensively reviewed, and all available data supplied in reported cases of this syndrome were analyzed. The figures presented under this group heading include a total experience with 325 instances of idiopathic pericarditis, reported from multiple sources. Care was taken to avoid inclusion of "repeat" cases in subsequent reports of various groups. With two exceptions, the reports analyzed were all subsequent to 1948. This group is hereafter referred to as the *collected AIP group.*

Group D: The literature relating to DLE was also reviewed, but without specific reference to the clinical presence of acute pericarditis, since such data are not commonly presented by authors. Therefore, this group does not equate with our DLEP group. The figures for this group are offered as a percentage range, since the particular interest of authors dealing with DLE tends to affect the specific percentages considerably. The survey includes some 591 reported cases of DLE.

All percentages given in the text and tables are derived from the total number of *positive* observations within the *total number* of such *observations* made for the finding under discussion, rather than from the total number of *cases.*

Occurrence and Frequency of Diagnostic Confusion Between DLE and AIP

Since vigorous control measures and adequate therapeutic agents have been applied to syphilis and tuberculosis, DLE has emerged as one of the candidates to supersede these diseases as "the great masquerader." Disseminated lupus is capable of presenting initially in any one of a variety of forms, each of which may provide, for a considerable period of time, the only overt manifestation of the disease. Just as the hematologist may be led a merry chase by an unexplained anemia or thrombocytopenia, or the rheumatologist be concerned with a protracted arthritis before the total picture finally unfolds, so may the cardiologist be called upon to bear witness to the fact that acute pericarditis may act as the "calling card" of DLE. To compound such problems, disseminated lupus has the well-known ability to undergo spontaneous remission and exacerbation in any one of its many possible zones of involvement. One such site of possible initial and recurrent involvement is the pericardium.

Turning to AIP, we find that substernal or precordial chest pain has become the virtual *sine qua non* for diagnosis—possibly because, without this symptom, the syndrome probably escapes detection except under the most fortuitous circumstances. The sudden appearance of severe chest pain in an apparently healthy individual, accompanied by a pericardial friction rub and electrocardiographic alterations compatible with pericarditis, usually suggests the entity of AIP to the physician after certain obvious causes for this chain of events have been excluded. Yet, we have found that disseminated lupus may present in an identical manner.

In our experience, some 91 per cent of patients with AIP have entered with the chief complaint of precordial or substernal chest pain. Others have noted an incidence ranging from 70 to 100 per cent. However, in 43 per cent of our DLEP group, such chest pain was also the symptom which led to admission and, in each instance, either a pericardial friction rub, electrocardiographic changes, or both were also present. The chances for diagnostic confusion

in such a patient with DLE are obvious. Indeed, in most of our DLEP patients with such a presentation an initial diagnosis of AIP was made.

Other authors have noted that DLE may present in this fashion, but we can offer no statistics regarding its incidence because of the retrospective nature of the reports dealing with DLE. However, in several series significant chest pain was noted to have occurred in 22 to 65 per cent of DLE subjects, and in a small segment this was apparently the presenting complaint.[1–3]

Obviously, if such a presentation is accompanied by the simultaneous presence of clinically apparent multiple organ involvement, diagnostic errors are not likely to occur. But pericarditis in DLE may occur at a time when one must resort to careful search for other manifestations of systemic involvement. Such search is not likely to be carried out unless it is recognized that DLE may bear a striking superficial resemblance to AIP.

Thus, while it is difficult to assess the incidence and duration of diagnostic error in other medical centers, a strong possibility appears to exist, on the basis of our experiences, that the masquerade of DLE as AIP is more than a theoretical possibility. To this point, we offer below three pertinent instances in which this diagnostic difficulty occurred.

CASE 1. M. S., a 44-year-old Negro female, was admitted to the District of Columbia General Hospital on December 9, 1955, because of arthralgia, chest pain, and fever.

Past history revealed that the patient had been hospitalized for the first time in 1933, because of an episode of fever, substernal chest pain, and dyspnea. The patient recalled that the chest pain had been intense and that much attention had been devoted to "listening to a noise over my heart." She had been told at that time that there was "fluid around [her] heart." Although she had been quite ill at the time of admission, the episode apparently resolved rapidly with no specific therapy, and the patient was asymptomatic when discharged. In 1946 and 1948 the patient had had two uneventful full-term pregnancies with uncomplicated hospital deliveries. Physical examination, hematocrit, white blood count, and urinalyses during these two obstetric hospitalizations had revealed no significant abnormality.

First Hospital Admission: The patient's first medical admission to the District of Columbia General Hospital, on February 12, 1953, was precipitated by severe substernal chest pain. During the week prior to admission she had noted fever, cough, malaise, some dyspnea, and migratory myalgia and arthralgia. On the day of admission, the patient had developed severe substernal chest pain, aggravated by respiration and movement. Physical examination revealed a temperature of 104°F, blood pressure of 115/75, pulse of 152/min, and respirations of 20/min. No objective joint abnormalities were present. There was dullness to percussion at both lung bases posteriorly. The area of cardiac dullness was markedly increased to the right and left. The second pulmonic sound was accentuated. A loud pericardial friction rub was present.

Laboratory Studies: The hematocrit was 34 per cent and the white blood count was 8,000/cu mm. An electrocardiogram showed classical ST-T changes of acute pericarditis. Chest roentgenogram demonstrated marked enlargement of the cardiac shadow and a large right and a small left pleural effusion. Bilateral thoracentesis yielded an exudative fluid containing a few polymorphonuclear cells, which proved sterile on culture. A skin test for tuberculosis was negative. Three days after admission, evidence suggesting pericardial tamponade led to pericardiocentesis yielding 370 cc of a sterile, serosanguineous fluid. A right scalene node biopsy revealed no significant abnormality on microscopic study. An LE preparation was unrewarding.

Clinical Course: The patient's symptoms underwent spontaneous improvement, with no specific therapy being employed. Serial electrocardiograms showed gradual reversion of ST-T changes toward normal. Fever abated after five days, and evidence of pericardial and pleural effusion regressed. Heart size returned to normal by chest roentgenogram. The patient was discharged during the third hospital week with the diagnosis of "acute idiopathic pericarditis."

Second Hospital Admission: The patient then remained asymptomatic until January 5, 1955, when she was seen in the outpatient clinic because of an episode of fever and substernal chest pain. Physical examination was within normal limits. Hospital admission was advised but was refused by the patient. She returned to the clinic one week later, stating that her symptoms had resolved in 48 hours.

On March 3, 1955, the patient was admitted to the surgical service with signs and symptoms of acute cholecystitis. Physical examination revealed a blood pressure of 110/80, pulse of 100/min, temperature of 102°F. Examination of the heart and lungs was unremarkable. The hematocrit was 31 per cent, the white blood count 8,700/cu mm. Urinalysis showed 3–4 white blood cells and 4–5 red blood cells/hpf, and 4+ proteinuria. Chest x-ray was unremarkable. Cholecystography demonstrated gallstones. Cholecystectomy was performed, from which recovery was uneventful.

Third Hospital Admission: The patient was admitted for the last time on December 9, 1955. During the previous three weeks she had experienced fever and tender swelling of multiple joints. On the day of ad-

mission, severe pleuritic and substernal chest pain had developed. Examination revealed a blood pressure of 90/60, pulse of 124/min, temperature of 104°F, and respirations of 24/min. The wrists, elbows, shoulders, and knees were hot, swollen, and tender. The area of cardiac dullness was markedly increased to the right and left. Physical evidence of bilateral pleural effusion was present, and hepato- and splenomegaly were detected.

An electrocardiogram showed low voltage and nonspecific T wave abnormalities. The hematocrit was 33 per cent and the white blood count 7,000/cu mm. The urine contained 4+ protein, numerous white cells, red cells, and hyaline casts. Total serum protein was 8.0 Gm/100 ml, with 2.8 Gm albumin and 5.2 Gm globulin per 100 ml. An LE test was again obtained and this time demonstrated several typical "L.E. cells."

Course: Despite intensive therapy, the patient's course was steadily downhill. Pleural and pericardial effusions were prominent features during the illness, necessitating several pleural and pericardial taps. Evidence of cardiac decompensation appeared and progressed, and the patient's renal function progressively deteriorated. The patient died on April 14, 1956. Permission for postmortem examination was denied.

Comment on Case 1

This patient apparently had her first episode of acute pericarditis with effusion some 22 years prior to the overt development of disseminated lupus. Three other bouts of acute pericarditis preceded the patient's death. Prior to the last admission, the patient appeared to represent a rather characteristic instance of acute idiopathic pericarditis. Recurrent pericarditis, which resolved on each occasion without apparent residual, seemed to meet the criteria for this diagnosis. Only events during the final admission indicated the true nature of the process.

CASE 2. C. J., a 25-year-old Negro female, was admitted to the District of Columbia General Hospital on December 8, 1956, with the complaint of substernal chest pain of two weeks' duration. Her past history was one of good health, aside from three pregnancies complicated by transient hypertension and edema.

About three weeks prior to admission the patient developed a slight nonproductive cough. Two weeks prior to admission she noted onset of a sharp substernal pain. This was intensified by respiratory movements and was somewhat relieved by sitting up and leaning forward. There was no intensification by swallowing, or any relation to exertion. The pain had continued to the time of admission. Aside from the pain, the patient had no complaints.

Physical Examination: Blood pressure was 165/95; pulse 92, with an occasional extrasystole; and temperature 101°F. The lungs were clear to examination. The heart was not enlarged. A normal sinus rhythm was interrupted occasionally by a premature beat. P_2 was greater than A_2. There was a grade 2 apical systolic murmur. A loud to-and-fro pericardial friction rub was heard along the right sternal border, maximal in the third and fourth interspaces. Remainder of the examination was unremarkable.

A chest roentgenogram demonstrated a normal cardiac contour and a small infiltration at the right base. An electrocardiogram showed left axis deviation, an occasional ventricular extrasystole, and nonspecific T wave abnormalities.

Prior to further laboratory tests, the impression existed that this was an instance of acute idiopathic pericarditis.

Laboratory Findings: Hematocrit, 26 per cent; white blood count, 7,400/cu mm; urinalysis, 4+ proteinuria, many white and red blood cells.

On the basis of these laboratory findings, an LE preparation was obtained. This was strongly positive.

CASE 3. B. L., a 31-year-old Negro female, was admitted to the District of Columbia General Hospital on March 4, 1957, with the diagnosis of acute idiopathic pericarditis having been made by her private physician. Past history was one of excellent health, aside from a cholecystectomy for cholelithiasis five years before.

The patient had felt well until the day of admission, when she suddenly developed a severe substernal chest pain which radiated to both pectoral areas. This was aggravated by deep inspiration but there was no relation to exercise, position, or swallowing.

Physical Examination: Blood pressure was 100/70; pulse rate 140; temperature 104.2°F; respirations 40. The patient appeared acutely ill, complained of substernal pain, and was tachypneic. The lungs were clear to examination. The area of cardiac dullness was enlarged nearly to the anterior axillary line on the left. There was a sinus tachycardia of 140. The second pulmonic sound was greater than the second aortic sound. A loud pericardial friction rub was audible along the lower left sternal border. There was some spotty depigmentation of the malar areas of the face. Remainder of the examination was unremarkable.

A chest roentgenogram revealed clear lung fields and a markedly enlarged cardiac shadow suggestive of pericardial effusion. An electrocardiogram demonstrated ST and T wave changes compatible with acute pericarditis.

On repeated questioning, the patient denied any symptoms prior to the onset of the chest pain and stated that the facial lesions had been present in their present form for "years." The initial clinical impression was "acute idiopathic pericarditis with pericardial effusion."

Laboratory Findings: Hematocrit, 28 per cent; white blood count, 11,400/cu mm; urinalysis, 4+ proteinuria, 3–4 red blood cells, and 4–5 white blood cells/hpf. PPD skin test for tuberculosis, negative. Venous pressure, 170 mm saline.

Because of the abnormal blood and urine findings, an LE preparation was obtained on the second hospital day. This was strongly positive. The patient subsequently required three pericardial paracenteses for relief of pericardial tamponade.

Comment on Cases 2 and 3

Both of these young women (cases 2 and 3) presented with "acute pericarditis." In neither case was there historical data which suggested lupus erythematosus. Physical examination was likewise not helpful in either instance. A malar rash in case 3 appeared to provide a valuable clue, although the statement by the patient that it had been there for a considerable interval tended to limit its diagnostic significance.

The similarity of these individuals when first seen to instances of acute idiopathic pericarditis was rather striking. However, the experience with the patient described previously and the markedly abnormal blood and urine data raised the immediate suspicion of disseminated lupus erythematosus as the etiologic basis of the pericarditis, a suspicion which was quickly confirmed.

Parallel Features of DLE and AIP

While the combination of a high index of suspicion and grossly abnormal laboratory values can lead to early separation of AIP and DLE, confusion may readily arise when either of these differential requisites is lacking. Unfortunately, organ involvement in one area is well known to frequently precede obvious disease of other systems in DLE. When such organ involvement selects the pericardium as its initial target, the parallel between DLE and AIP may be considerable (Table I).

Recurrence: Much stress has been laid upon the tendency to recurrence of "attacks" of AIP.[4,5] In our AIP series, some 13 per cent of the patients had one or more recurrences. Cumulative figures from the literature indicate a 16.6 per cent incidence of recurrence in AIP, a figure lower than might be expected in view of the emphasis given this feature of the syndrome.

It is of considerable interest to note the "other side of the coin;" namely, the incidence of recurrent pericarditis in patients with DLE as the underlying process. Four of our DLEP group (28.6 per cent) had had previous episodes of pericarditis. These preceded the development of other manifestations of DLE by periods ranging from $1^1/_2$ to 22 years. During this

TABLE I

Percentage Incidence of Parallel Features in Acute Idiopathic Pericarditis (AIP) and Pericarditis of Disseminated Lupus Erythematosus (DLEP)

Case source	No. cases	Chest pain					Average age at onset (yrs)	Race (% white)	Fever (over 100 °F)	Tachycardia (pulse over 100/min)
		Recurrence	Frequency	Radiation to abdomen	Aggravated by swallowing	As presenting complaint				
AIP (Authors)	23	13	91	None	8.7	91	36	17.4	48	35
AIP (Lit.)	325[a]	16.6	96	11.7	5.0	96	38	9.0	70	49
DLEP (Authors)	14	28.6	50	28.6	None	43	38	7.0	36	43
DLE (Lit.)	591[b]	—	0–65	—	—	—	3–73	52–100	86–100	—

Case source	No. cases	Pericardial friction rub	Pericardial effusion	Pulmonary infiltration	Pleural effusion	Electrocardiogram		
						Classical ST-T changes	Nonspecific ST-T changes	No abnormality
AIP (Authors)	23	61	48	33	18	75	17	8
AIP (Lit.)	325	74.8	54	28	31	63.8	30	6
DLEP (Authors)	14	35.7	72	29	43	38.5	43	18.5
DLE (Lit.)	591	2–18	5.7–8	21	24–56	—	—	—

[a] Reference numbers 4, 5, 10, 11, 14–22, 24–29, 33, 43, 44, 51–58.
[b] Reference numbers 1, 2, 7–9, 13, 23, 50, 59, 60.

initial episode of pericarditis, the diagnosis of lupus was established during hospitalization in only one patient. In the other three instances, the patients were discharged as instances of AIP. The correct diagnosis was made only after a recurrence of pericarditis, usually associated with other symptoms of the disease, had prompted readmission to the hospital. Meachum has reported a case in which a similar sequence of events was noted.[6]

Since our experience indicates that individuals with DLE may mimic the "characteristic recurrent course" of AIP, we would regard such patients as DLE suspects until time or repetitive and careful evaluation has ruled out this possibility.

Chest Pain: Some form of chest pain is common in both AIP and the pericarditis accompanying lupus. In our AIP group, 91 per cent had significant chest pain, while our DLEP group showed a 43 per cent incidence. The collected group of AIP patients demonstrated this symptom in 96 per cent of the cases. In both the AIP and DLEP groups, the pain was frequently pleuritic in nature and radiation to the left shoulder was not uncommon. The pain in the DLEP group differed, however, in the high incidence of radiation of pain to the abdomen and the total absence of aggravation by swallowing (see Table I).

While neither the presence nor the nature of chest pain can be used to distinguish AIP from DLEP, its lower incidence in the latter state is of interest. It has been noted by several investigators that the great majority of patients with DLE have microscopic evidence of pericarditis at postmortem, although chest pain frequently had not been noted during life.[3,7–9] This same situation applies to rheumatic, uremic, and tuberculous pericarditis; i.e., a low incidence of chest pain relative to the frequency with which pericardial inflammation is found at postmortem. This paradox suggests that a *selection* of the patients labeled as AIP may occur on the basis of the presence of chest pain, while the relatively painless cases escape medical notice. This concept of "selection by chest pain" in AIP gains support from other pathologic studies indicating that many individuals with evidence of old or recent pericarditis at postmortem examination have had no clinically apparent pericardial disease during life.[7,10,11]

Age of Onset: Both DLE and AIP occur predominantly in the younger age groups. The average age in our AIP group was 36 years; in our DLEP group, 38 years; and in the collected AIP group, 38 years. In the combined series of Harvey[7] and Dubois,[12] the average age of patients presenting with DLE was 28 years. Well over 50 per cent of the cases in all groups fall between the ages of 20 and 40, although the extremes of age are noted occasionally with either disease state.

Race: While 82.6 per cent of our AIP series and 93.0 per cent of our cases of DLEP were nonwhite, this is undoubtedly only a reflection of our predominantly nonwhite hospital population. Indeed, in reported series of DLE, Jessar[13] has noted 91 per cent and Harvey[7] 84 per cent of their cases in whites. AIP is known to occur without significant reference to race, though insufficient data are available for statistical analysis. Thus, racial distribution cannot be used to separate the disorders.

Fever: A temperature over 100°F occurred in 48 per cent of our AIP group, in 36 per cent of the DLEP patients, and in 70 per cent of AIP cases in the literature. In several series of DLE, the incidence of fever ranged from 86 to 100 per cent.[2,7,12,13] In both conditions, the degree of fever may range widely, and we have noted oral temperatures exceeding 103°F in several patients with both diseases. However, in DLE the temperature tends to be more prolonged, and persistence of fever beyond 7 to 10 days in AIP suggests that some specific form of pericarditis exists.

Tachycardia: A pulse rate above 100 was noted in 35 per cent of the AIP group. In general, tachycardia appears to parallel the degree and incidence of fever, but in DLE it may be indicative of myocardial involvement.

Pericardial Friction Rub: This pathognomonic sign of pericardial involvement does not serve to distinguish patients with DLE from those with AIP, although the reported incidence is considerably higher in the latter group (see Table I). It is probable that the high incidence of this sign in AIP partially reflects the frequency and care with which it is sought when the diagnosis of AIP is entertained.

Pericardial Effusion: Evidence indicative of pericardial effusion is frequent in both conditions under discussion. Of our AIP patients, 48 per cent demonstrated this abnormality, while 72 per cent of the DLEP group and 54 per

cent of the collected AIP cases also had evidence supporting such a diagnosis.*

While extensive pericardial effusion is somewhat more common in patients with DLE than in AIP, this finding has no differential value. In both conditions, pericardial fluid may accumulate with sufficient rapidity to produce the medical emergency of cardiac tamponade. A number of such cases have been described by those dealing with AIP,[18–21] and Shumacker[10] reported two instances in which pericardiectomy was carried out because of recurrent pericardial effusion. Furthermore, of the seven deaths reported in AIP, five were related to tamponade.[11,18,21–24]

Although tamponade is less frequent in DLE, Contro[26] has described a case of this type, and we have encountered two such patients. One patient required such frequent pericardiocenteses for relief of tamponade that a pericardial "window" was finally established surgically.

Examination of the pericardial fluid does not permit differentiation of AIP from DLE, unless a positive "LE prep" is obtained from such material.[1] Of the reported cases of AIP, 10 per cent[31] have had productive pericardial taps. The fluid was serous in 14,[10,14,18,20,25,26] serosanguineous in 7,[18,21,22,27] and not described in 10. The fluid was exudative in nature in all described instances, as indicated either by high specific gravity or total protein content.[10,20,26,28,29] The white cell count was highly variable both numerically and in cell type.[10,28]

The pericardial fluid obtained in DLE is also subject to a wide range of appearance and composition. It is most often exudative in nature, may vary from serous to serosanguineous, and may contain a variable number of white blood cells.

In our series, pericardiocentesis was performed in two patients with AIP and three with DLEP. The fluid in AIP was serosanguineous in one, serous in the other. In both it was exudative and contained a small number of lymphocytes. In DLEP, the fluid was serosanguineous in one and serous in a second. The third patient showed a grossly purulent, thick pericardial fluid on three successive pericardial taps done to relieve pericardial tamponade. The white count exceeded 25,000/cu mm on all three occasions and was chiefly polymorphonuclear. The fluid was consistently negative for bacteria, fungi, and tubercle bacilli on culture, but did yield a positive LE cell preparation.

Pulmonary Infiltrate: Pulmonary infiltration is a common finding on roentgenogram in both AIP and DLE. We found such an abnormality in 33 per cent of our AIP patients, 29 per cent of our DLEP patients, and 28 per cent of the collected AIP cases. In various series of DLE, the incidence of such infiltration has ranged from 20 to 22 per cent.[7,13]

In both disorders, the infiltration varies in extent and duration. Some workers have noted the more frequent involvement of the left lung in the face of AIP, the reason for such apparent localization being unclear. In DLE, the "pneumonitis" may present in a transient, focal interstitial form[30] or as an extensive, persistent consolidation.[2,31]

The frequency of pulmonary infiltration in AIP has often been taken as evidence for a relationship between the viral ("primary atypical") pneumonias (PAP) and AIP, and such a conclusion may be valid in a certain percentage of cases.[15,32–34] Several reports of "simultaneous" PAP and AIP have been reported, and one of us (K.M.M.) has noted such an instance with diagnostic elevation of cold agglutinins. However, Dressler[35] has indicated that "pneumonitis" may also occur in the postcommissurotomy and postmyocardial infarction syndromes and has therefore related all of these conditions, including AIP, to a "hypersensitive" etiology.

Therefore, the finding of coincident pericarditis and pneumonitis is of little diagnostic aid, as it may occur in a wide variety of disorders.

Pleural Effusion: Pleural effusion is a common occurrence in both diseases under discussion. In our series, 43 per cent of patients with DLEP demonstrated pleural fluid by roentgenogram. Dubois[12] cites an incidence of 55 per cent in 62

* The difficulty in differentiating pericardial effusion from cardiac dilatation is widely appreciated. Those who suggest that the enlarged cardiac silhouette is due to dilatation cite the lack of signs of cardiac compression, the usually normal electrocardiographic voltage, the normal cardiac sounds, and the electrocardiographic evidence of "myocardial" involvement.[14–17] The group favoring pericardial effusion points to the frequency with which fluid is discovered by pericardiocentesis at surgery or postmortem in instances classified as "probably dilatation." Certainly, the most reliable sign remains the rapid change in cardiac size on serial roentgenograms.

TABLE II

Percentage Incidence of Divergent Features in Acute Idiopathic Pericarditis (AIP) and Pericarditis of Disseminated Lupus Erythematosus (DLEP)

Case source	No. cases	Antecedent upper respiratory infection	Gastrointestinal symptoms	Sex (females)	Hypertension (above 150/90)	Congestive heart failure	Skin rash	Lymphadenopathy
AIP (Authors)	23	52	13	16	8.7	13	None	None
AIP (Lit.)	325	53	56	15	—	14.4	—	—
DLEP (Authors)	14	7	21	86	43	78.5	50	21.4
DLE (Lit.)	591	—	20–35	85–98	20–30	8–24	52–91	34–68

Case source	No. cases	Hepatomegaly	Splenomegaly	Leukocytosis (WBC over 10,000)	Leukopenia (WBC under 5,000)	Urine abnormalities	Elevated serum globulin	Positive serologic test for syphilis
AIP (Authors)	23	17.5	None	52.3	9.5	5	None	19
AIP (Lit.)	325	—	—	54	3.6	<1	—	—
DLEP (Authors)	14	64.2	14.4	28.6	35.7	78	50	50
DLE (Lit.)	591	29–44	8–40	31	68–74	57–70	42–69	18–44

cases of DLE, while a slightly lower figure is mentioned by others.[2,13]

In AIP, 18 per cent of our patients had this abnormality, while the incidence in the cases reviewed reached 31 per cent. It is likely, however, that pleuritis without recognized effusion is present in a considerably larger percentage, since it has been indicated that the "typical pain" of AIP is closely related to pleural inflammation.[36]

The nature of the fluid obtained from thoracentesis is of no diagnostic aid unless LE cells are found in such fluid.

Electrocardiogram: The electrocardiogram is of no aid in differentiating the two forms of pericarditis, as might be expected, since the pathologic substrates of the electrocardiographic abnormality are undoubtedly similar.[37,38] While classical ST segment and T wave changes are more frequently noted in AIP, these are not uncommon in the DLEP group. Such classical patterns were present in 75 per cent of our AIP group, 38.5 per cent of our DLEP group, and 63.8 per cent of the collected AIP group. "Nonspecific" abnormalities of ST segment or T wave are more often encountered in DLEP, possibly because of the frequency with which true myocardial involvement appears in this disease.[8]

The electrocardiographic pattern seen in pericarditis is known to depend upon the point in time at which the tracing is taken. Therefore, it is probably a tribute to the severity of the pain in AIP that so many individuals are seen at an early phase when classic ST-T changes are present, rather than a manifestation of any innate difference between basic tissue involvement in this form versus other forms of pericarditis.[38]

Divergent Features of AIP and DLE

It is apparent from the data presented in the preceding section that individuals with pericardial involvement as a manifestation of DLE may present features leading to the erroneous diagnosis of AIP. However, our experience has indicated that such errors may be promptly remedied if the areas in which the two entities tend to *diverge* are kept in mind from the outset (Table II).

Antecedent Upper Respiratory Infection: This symptom is of value when present, for it is an uncommon prelude in patients with pericarditis due to DLE. Only 7 per cent of our DLEP patients had an antecedent upper respiratory infection, while 52 per cent of our AIP cases and 53 per cent of the collected AIP cases had such a history. It is apparent that the *absence* of an antecedent respiratory infection is of no diagnostic aid.

Gastrointestinal Symptoms: Nausea, vomiting, diarrhea, abdominal pain, and other gastrointestinal complaints were more frequent in the DLEP group (21 per cent) than in the AIP group (13 per cent).

Other authors indicate that individuals with DLE are considerably more prone to manifest gastrointestinal symptoms than those with AIP. While Powers[44] has indicated that such symptoms may occasionally be quite striking in AIP, the incidence of GI complaints in the collected series of AIP reaches only 5.6 per cent and rarely are these the presenting symptoms. On the other hand, Dubois[12] had reported that 10 per cent of his cases of DLE offered a chief complaint of gastrointestinal nature and 40 per cent had some form of gastrointestinal disturbance. Shearn and Pirofsky[2] noted such symptoms in 50 per cent of DLE patients.

The rather high incidence of gastrointestinal symptoms in DLE can be correlated with postmortem demonstration of vascular lesions of the bowel wall and inflammatory changes in the intra-abdominal serous membranes.[2,12,13,33] Their source in AIP is less well defined, since the limited pathologic material available has revealed no specific lesions of the gastrointestinal tract.

Sex: Statistically, the sex of the patient may offer a valuable clue, since it has been well documented that DLE has a marked preference for the female. Females comprised 86 per cent of our DLEP series, while Jessar[13] reported 98 per cent females in his series and 85 per cent in the total of 367 cases which he culled from other sources. The sex incidence in AIP is almost the reverse, with 84 per cent of our AIP patients and 85 per cent of those reported in the literature being males. Obviously, the female with pericarditis of unknown cause is a DLE suspect until this diagnosis has been carefully excluded.

Hypertension: The simple maneuver of blood-pressure measurement provides a valuable piece of differential evidence, with the presence of hypertension favoring DLE. In our series only 8.7 per cent of AIP cases demonstrated a systolic pressure above 150 mm Hg or a diastolic pressure above 90 mm Hg, while these pressures were found in 43 per cent of the DLEP group.

Most reviews of AIP make no mention of the presence of arterial hypertension. Conversely, in DLE between 20 and 30 per cent of patients have been found to be hypertensive. It is presumed that this difference in arterial pressure is, at least in part, a manifestation of the high incidence of renal involvement in DLE and its absence in AIP, since each disease is most common in the younger age groups where a low incidence of hypertension is normally expected.

Congestive Heart Failure: A clinical diagnosis of congestive heart failure was made in only 13 per cent of our patients with AIP, but in 78.5 per cent of those with DLEP. Our incidence of failure in the idiopathic group parallels that collected from the literature of 14.4 per cent. This is a surprisingly large figure, since cardiac failure is not commonly thought to be an accompaniment of "benign" pericarditis.

The frequency of cardiac failure in our lupus patients (78.5 per cent) is considerably higher than that reported (8 to 24 per cent) by other observers.[2,7,12,13] Since evidence of valvular disease, pericardial tamponade, or prolonged hypertension was lacking in virtually all of these individuals with clinically defined heart failure, it would appear that myocardial disease was the pathogenetic basis of their failure. Thus, the occurrence of *overt* pericarditis in DLE may carry with it the same prognostic implications as its occurrence in the rheumatic subject in whom such a finding usually connotes the presence of a rather severe form of carditis.[45]

Skin Rash: None of our patients with AIP had a significant dermatologic lesion, nor have any of the cases collected. In our DLEP group, however, 50 per cent had some form of skin eruption. Others have mentioned an incidence of 52 to 91 per cent of lupus subjects with dermatologic involvement.[2,7,12,13] The implication is clear. The presence of a skin lesion in an individual with acute pericarditis should call immediate attention to the possibility of DLE, regardless of history or other data which initially suggest that "idiopathic" pericarditis is present.

Lymphadenopathy: Generalized lymphadenopathy was noted in 21.4 per cent of our DLEP cases, but was absent in all AIP patients. Its incidence in other series of AIP is neglected, but in DLE it is a common event, ranging from 34 to 68 per cent.[2,7,12,13]

Hepatomegaly: Liver enlargement was frequent in our patients with DLEP, some 64.2 per cent showing this abnormality, in contradistinction to the AIP patients, in only 17.5 per cent of whom was hepatomegaly present. The occurrence of hepatic enlargement in both groups ap-

peared related to the presence of clinical congestive heart failure.*

The incidence of hepatic enlargement is rarely commented upon in other series of AIP and may be assumed to be low. In DLE, from 29 to 44 per cent have demonstrated hepatomegaly.

Splenomegaly: The finding of splenomegaly in patients with acute pericarditis is of some differential value. Some 14.4 per cent of our patients with DLEP had splenic enlargement, while none of those with AIP had this abnormality. Mention of splenomegaly in other series of AIP is lacking. In DLE, splenomegaly has been noted in 8 to 40 per cent of the cases.

White Blood Count: A white blood count below 5,000/cu mm was approximately four times more common in DLEP than in AIP (35.7 per cent vs. 9.5 per cent). Reference to the literature shows an even wider divergence, with leukopenia being reported in 68 to 74 per cent of lupus patients[2,7,12,13] and in only 3.6 per cent of persons with AIP. Thus, the presence of leukopenia is of some diagnostic significance in differentiating between the two conditions.

A white blood count above 10,000/cu mm was encountered twice as frequently in AIP (52.3 per cent) as in DLEP (28.6 per cent). In the latter group, leukocytosis was usually associated with the presence of concurrent infection.

Anemia: A hematocrit below 35 was arbitrarily selected as the point below which anemia was present. The difference between the two patient groups with respect to this parameter was striking. Eighty-six per cent of patients with DLEP were anemic by this criterion, while only 13 per cent of our AIP patients fell into this category. Furthermore, 67 per cent of the lupus patients had hematocrit values below 30, and 17 per cent below 20. In the AIP group, all anemic patients were female, and in no instance was the hematocrit below 30.

Urinary Abnormalities: Patients were classified as having abnormal urinary findings if the test for protein was 2+ or more, and red cells and/or casts were present in the sediment. The division between the two groups was quite sharp. Seventy-eight per cent of the DLEP group had such urine abnormalities, while only 5 per cent of those with AIP fell into this category. As best as can be determined from the literature, abnormal urine sediment (by our criteria) has been noted in from 57 to 70 per cent of patients with DLE,[2,7,12,13] but in less than 1 per cent of those with AIP. It is apparent that examination of the urine may provide one of the most valuable immediate clues to the fact that one is not dealing with an instance of acute idiopathic pericarditis.

Serum Proteins: A globulin above 3.5 Gm/100 ml was considered abnormal and patients were compared according to this criterion. The difference was a distinct one, with 50 per cent of the DLEP patients showing globulin figures above this level, while all AIP patients had values below 3.5 Gm/100 ml. The increased globulin content in patients with DLE has been shown by several investigators to reside in the gamma fraction[46,47] and is felt to play a role in both the biologic false-positive serologic test for syphilis and the formation of the characteristic LE cell. Idiopathic pericarditis is not associated with any of these phenomena.

Serologic Test for Syphilis (STS): The biologic false-positive STS in DLE has become recognized as a frequent hallmark of the disease,[48] especially since the treponemal immobilization test (TPI) has made it possible to confirm that a large percentage of these standard serologic tests were in error.[49] In our series, a 50 per cent incidence of positive serologic tests for syphilis (VDRL) was encountered in the DLEP group. In four instances, TPI tests were done and three of these were negative. Other investigators report an incidence of false-positive STS in DLE ranging between 18 and 44 per cent.[2,3,12,50]

By comparison, a positive STS was obtained in 19 per cent of the patients with AIP, an incidence which parallels that expected in our hospital population.*

LE Tests: Obviously, the most specific diagnostic test available for differentiation between AIP and DLEP is performance of one of the standard "LE cell tests." However, some comments relating to this test are in order. First, the findings of a negative "LE prep" in a patient with pericarditis is not final assurance that lupus is not present. We and others[7,12] have encountered patients who developed the classical clinical features of DLE and presented the characteristic lesions at postmortem, although one or more "LE

* Since postmortem studies have indicated that the hepatic changes in DLE are predominantly those of fatty degeneration and cellular necrosis, hepatomegaly cannot be attributed to the occurrence of congestive heart failure alone.[2,7,12,13]

* It is to be borne in mind, of course, that there are nearly 20 varieties of disease which may be associated with a biologic false-positive STS in addition to DLE.[51]

preps" had been negative during life. It is now appreciated that a single "LE prep" merits repetition in any instance where DLE is strongly considered, since further search may bring the reward of a positive test. Finally, there is evidence indicating that the "LE test" may remain negative for a variable period of time despite the presence of other evidence indicating activity of the DLE process.

With these considerations in mind, it is most interesting to note the extreme infrequency with which "LE tests" have been done in patients with AIP. Only 1 per cent of the cases of AIP reviewed had an "LE test" as part of their diagnostic evaluation, and only two patients in our series were so tested. It would seem advisable to institute the routine performance of an "LE test" in all patients regarded as having AIP, until an adequate experience regarding this point is available. Such a routine has been put into effect at this hospital.

Mortality: The widely divergent prognosis between DLE and AIP provides sufficient reason for attempting early differentiation of these entities, especially if there be merit in prompt institution of therapy in DLE. Of our DLEP patients, 42.9 per cent have died up to the time of this report. None of the patients with acute idiopathic pericarditis has died.

Harvey[7] has analyzed the mortality data in DLE extensively and has indicated that 13 per cent are dead within the first 3 months after diagnosis, 22 per cent after the first year, and 48 per cent by the end of four years. Even this analysis is somewhat more hopeful than that of Jessar[13] which indicated a 38 per cent survival for four years.

AIP, however, is not a benign condition in all instances. Approximately 2 per cent of the collected cases of AIP have terminated fatally, with virtually all patients having succumbed to pericardial tamponade. It would appear that mortality in AIP can be virtually eliminated if the physician is alert to the development of this complication.

Discussion

While much descriptive verbiage has been lavished upon the syndrome known as AIP, it must be recognized that the distinguishing feature of AIP is *not* the type of chest pain, the presence of a friction rub, or a particular electrocardiographic pattern—rather, its central feature is the *inability of the physician to demonstrate an etiologic basis for the observed symptoms and signs.* Therefore, AIP is a diagnosis of exclusion. As such, the diagnosis of AIP should not be applied to any individual with acute pericarditis until the many entities capable of producing pericardial inflammation have been carefully evaluated.

Although such statements may seem to represent emphasis of the obvious, they are pertinent to this discussion since there is a tendency in many quarters to employ the diagnosis of AIP without adequate search for possible etiologic factors. The infrequency with which tuberculin and other skin tests, cold agglutinins, LE tests, and attempts to isolate viral agents have been carried out in such patients indicates that diagnostic ardor is dampened when the label "AIP" is applied to a patient with acute pericarditis of unknown cause. Such a practice has probably led to the inclusion of several pathogenetically different entities under the blanket term "acute idiopathic pericarditis."

One of the disease entities which may present in the form of AIP is disseminated lupus erythematosus with pericarditis. As we have indicated, this masquerade may be a most convincing one, with the existence of DLE being undetected for weeks to years. The duration of such diagnostic confusion is related to three major factors: (1) the extent to which other systems are involved by DLE at the time pericarditis develops; (2) the index of suspicion of the physician—i.e., his awareness of the many possible parallels between the two states; and (3) the corollary to such awareness—appreciation of the need for an intensive effort to exclude DLE and other instigators of pericarditis before the label "AIP" is applied.

The parallels between DLEP and AIP include a number of features in the history and the physical and laboratory examinations. A history of recurrence, which has been stressed as characteristic of AIP, may be noted in both entities. Patients with both diseases frequently first seek medical attention because of severe chest pain, the character of which provides no differential clue. Fever, tachycardia, and a pericardial friction rub are findings common to both DLE and AIP. Each disease tends to occur in relatively young persons with a prior history of good health. Pericardial and pleural effusion may be encountered with both, and the character of the fluid obtained at pericardiocentesis or thoracentesis has no diagnostic potential unless LE

cells are found. Zones of pulmonary infiltration may be noted with either form of pericarditis. The electrocardiographic changes are those of pericarditis, regardless of its pathogenetic basis.

Thus, the initial history and examination of the heart and lungs may be virtually identical in the two conditions. Evaluation which ends here increases the probability of diagnostic error. However, the data presented above have clearly indicated that when attention is paid to *details* of history and physical examination, one will uncover a number of valuable clues suggesting that the patient is a victim of DLE rather than AIP.

The 4:1 predilection of DLE for the female, and the nearly inverse ratio favoring the male in AIP, makes any female with acute pericarditis an immediate DLE suspect. The historical detail of an upper respiratory infection preceding the pericarditis, on the other hand, may suggest that AIP is statistically more likely. Prominence of gastrointestinal symptoms would be unusual in AIP. On physical examination, the presence of hypertension, congestive heart failure, a skin rash, lymphadenopathy, hepatomegaly, or splenomegaly all would heavily favor a diagnosis of DLE and should lead to further consideration in a patient believed to have acute idiopathic pericarditis.

Perhaps the most significant means of separating these two disorders is provided by the simple medium of the routine complete blood count and urinalysis. Discovery of leukopenia, anemia, or an abnormal urinary sediment may provide the first clue to the presence of DLE. Therefore, a low white blood count or a "few red blood cells" in the urine should be paid proper diagnostic respect. Where question exists, the laboratory examination should be repeated. Indeed, it is probably advisable to repeat urinalysis in any patient with acute pericarditis since (1) an abnormal urinary sediment is often the most compelling reason for looking beyond the diagnosis of AIP and (2) sediment abnormalities may be intermittent in DLE.

Each patient with AIP also merits a serum protein determination, since the finding of an elevated globulin fraction is of differential value. Furthermore, when a positive serologic test for syphilis is obtained in the absence of positive history, or when other features suggest the possibility of DLE, a treponemal immobilization test should be considered.

Lastly, if an individual with AIP presents any features suggesting the possibility of DLE, a "LE cell preparation" should be obtained. When pleural or pericardial fluid is removed in such cases, a portion of such material should be searched for cells exhibiting the LE phenomenon, since polymorphonuclear cells in such fluid have been suspended and well incubated in the patient's serum prior to their removal from the body.

Obviously, those features which separate DLE from AIP are manifestations of the major difference between the two syndromes—one is viewed as primarily a "local" or limited disorder, while the other is characterized by multiple system involvement. Therefore, when a patient diagnosed as having AIP presents evidence of disease beyond the pericardium and lung, the validity of this diagnosis is in jeopardy, and further search is in order for DLE or other disease processes.

It is our present feeling that a detailed medical search should be carried out in each patient with AIP. As indicated by our initial remarks, there is strong reason to suspect that multiple etiologic factors may be capable of producing the syndrome now called AIP. Virtually neglected in the past have been studies relating to the possible role of viral and fungal agents in producing this picture, and the role of the tubercle bacillus in certain acute and chronic instances of pericarditis is still not completely clear. The postmyocardial infarction syndrome and the variable syndromes loosely categorized as the "allergic vasculitides" must also be borne in mind.

It is apparent that there can be no contentment with a diagnosis of acute idiopathic pericarditis. Such lack of etiologic definition carries with it the corollaries of therapeutic impotence and prognostic error. Neither of these is acceptable, even though one may take some refuge by stating that individuals with AIP may weather their disease without apparent residual malfunction. However, it is difficult to convince a patient subject to recurrent episodes of AIP that his disease is "benign" and little cause for real concern. Furthermore, contentment with a label rather than an explanation has the unfortunate effect of inhibiting enthusiasm for investigative effort, since a feeling arises that such a label somehow provides explanation enough.

We have stressed here those features whereby patients with DLE may be quickly "plucked"

from the diagnostic wastebasket of AIP. It is to be hoped that future investigative attempts will lead eventually to complete emptying of this wastebasket.

Summary

(1) The group of patients upon whom the diagnosis of "acute idiopathic pericarditis" is presently conferred is probably a heterogeneous "wastebasket" encompassing several etiologic subgroups. It is proposed that disseminated lupus erythematosus with pericarditis provides one such etiologic segment.

(2) It is indicated that this masquerade of "lupus pericarditis" as instances of "acute idiopathic pericarditis" may be quite convincing and the underlying process may escape detection for a considerable period.

(3) Data are presented which indicate the major parallels between the two disorders. These may lead to an erroneous diagnosis of "idiopathic" pericarditis unless diagnostic caution is exercised.

(4) The major divergent features of the two disorders are analyzed in detail. Attention to these historical, physical, and laboratory dissimilarities should allow rapid detection of those patients whose pericarditis is due to disseminated lupus.

(5) Since disseminated lupus probably accounts for a small percentage of cases currently labeled "idiopathic pericarditis," further investigative effort is required to achieve total fragmentation of this entity into its allergic, viral, bacterial, and fungal components.

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Postviral Myopericarditis Associated with the Influenza Virus

Report of Eight Cases*

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ACUTE "nonspecific" or "idiopathic" pericarditis was first reported by Hodges[1] in 1854. Although the clinical features of this illness are well documented, there has been no consistently associated etiologic agent. The disease is characteristically preceded for one to two weeks by a distinct respiratory infection.[2–9] The pericarditis then begins suddenly with an episode of substernal pain, followed by fever, pericardial friction rub, and occasionally a pericardial effusion.[2–10] The clinical course lasts from a few days to several weeks.[4,5,7,8,9,11,12] The disease is by no means always "benign" and may be associated with pleurisy, pneumonitis, pleural effusion, myocarditis,[5,8,9,10,13,14] and on occasion it may result in death.[8,15–18]

This disease may easily be confused with acute myocardial infarction,[19–21] mediastinal emphysema, pleurisy,[22] pulmonary infarction, or spontaneous pneumothorax. The clinical appearance may also be confused with the signs of cardiospasm, diaphragmatic hernia, other types of pericarditis,[22] a variety of radicular pain syndromes, and gastrointestinal disorders.[23]

Several explanations of the pathogenesis of this form of pericarditis have been proposed. It has been suggested that this is a consequence of a viral infection[13,14,24–34] because of the common association of an upper respiratory infection a short time prior to the development of the pericarditis, and because of the failure to demonstrate significant bacterial pathogens in cultures obtained from the upper respiratory tract, blood, and pericardial and pleural effusions. The characteristic polymorphonuclear leukocytosis has previously been emphasized as an argument against a viral etiology; however, this sign may be a reflection of myocarditis similar to the leukocytosis found with acute myocardial infarction.

The interval between the primary respiratory infection and the subsequent pericarditis suggests a similarity to several other postinfection sequelae, such as glomerular nephritis and rheumatic fever which seem related to bacterial infection through an allergic or hypersensitive mechanism. An allergic or sensitizing reaction with involvement of the pericardium on the basis of a bacterial antigen has been advanced as a possible cause of "nonspecific" pericarditis.[26,28,35–37]

Infection with the tubercle bacilli[38,39] and other specific pathogenic bacteria[40] has been suggested as the cause. The disease has also been viewed as a variant of rheumatic fever.[1,37]

In 1957 Kagan and Bernkopf[41] reported a case of acute pericarditis with recovery after six weeks. Coxsackie virus group B, type 3, was isolated from the pericardial fluid and from the stools. More recently Weinstein[42] found Coxsackie virus group B, type 5, in association with an instance of acute "benign" pericarditis. In 1958, Movitt *et al.*[43] reported two similar cases of pericarditis associated with both group A and group B Coxsackie viruses, and to date there are twelve reported cases of fatal myocarditis and pericarditis associated with the group B Coxsackie virus.[44–49] Silber[33] reported two patients with acute "nonspecific" pericarditis in which a fourfold rise in antibody titer from influenza, type B, was demonstrated.

These observations are of particular interest because during the epidemic of influenza of 1957–58 in the United States, we saw eight pa-

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TABLE I

Summary of Clinical and Laboratory Findings in 8 Cases of Postviral Myopericarditis

Case No.	Age/ sex	Pneu-monia	Pleural effusion	Myo-carditis	Daily SGO-T	Cardiac enlarge-ment (by X-ray)	Pericardial rub	ECG evidence of pericarditis and myocar-ditis		C-reactive protein	Influenza vaccine	Fourfold or greater rise of influenza antibody titers	Follow-up
								ST	T				
1 (B. K.)	32/F	No	Yes, left	Yes	10 <10	Yes	Yes; grade 4, 10 days	+	+	3+	0	Type B (Great Lakes)	Mild recurrent chest pain 6 months; asymptomatic for 2 months
2 (H. G.)	48/M	Yes, LLL	Yes, left	Yes	14 74 66 19	Yes	Yes; grade 4, 7 days	+	+	4+	Type A (Asian) Oct. 57	Type B (Great Lakes) Type A (Jap)	Complete recovery; asymptomatic for 7 months
3 (G. M.)	43/M	No	No	No	17 27 24	No	Yes; grade 1, 2 days	0	+	0	0	Type B (Great Lakes)	Complete recovery; asymptomatic for 6 months
4 (A. B.)	59/M	No	No	No	72 42	No	Yes; grade 1, 2 days	+	0	0	0	Type B (Great Lakes)	Complete recovery; asymptomatic for 6 months
								Incomplete A-V block					
5 (R. T.)	42/M	No	No	No	—	No	Yes; grade 4, 7 days	+	+	3+	0	Type B (Great Lakes) Type A (Jap)	Complete recovery; asymptomatic for 7 months
6 (R. N.)	31/M	Yes, LLL	Yes, left	Yes	23 67	Yes	Yes; grade 2, 14 days	+	+	3+	0	Type A (Jap)	Recurrence of symptoms for 8 weeks; asymptomatic for 4 months
								Paroxysmal atrial fibrillation					
7 (E. C.)	38/M	No	No	No	14 10	No	Yes; grade 1, 4 days	0	+	0	Type A (Asian) Oct. 57	Type B (Great Lakes)	Complete recovery; asymptomatic for 4 months
								Low-voltage					
8 (P. H.)	15/M	No	No	Yes	36 42	Yes	Yes; grade 2, 2 days	+	+	3+	0	Type A (Jap)	Excellent response to steroid therapy with recovery
								Incomplete A-V block					

tients with acute "nonspecific" pericarditis that satisfied the clinical criteria. All these patients demonstrated at least a fourfold rise of serum antibodies against the influenzal virus while under observation. It appeared that the acute pericarditis was a sequela of influenza. The evidence to support this conclusion is summarized in Table I.

Case Histories

Case 1. B. K., a 32-year-old pregnant housewife, was admitted to the obstetrical service of St. Thomas Hospital on September 20, 1957, with complaints of "headaches, shortness of breath, swelling of the ankles, and elevated blood pressure" of three days' duration. The pregnancy was at term and had been uneventful except for a "bad cold" one week prior to the present illness. After induction of labor, the patient delivered a normal female baby weighing 7 lb 10 oz without difficulty. On the following day the mother complained of a severe headache, nausea, chest pain, and mild shortness of breath. The temperature, pulse, and blood pressure (146/96), remained at about the admission levels until three days postpartum, when the dyspnea increased and severe excruciating, substernal pain developed, radiating to the left arm along the ulnar distribution. The patient had not received influenza vaccine.

On physical examination the blood pressure was found to be 150/90, the pulse 100, and the temperature 101°F. The patient was orthopneic, and the respirations were rapid, shallow, and painful at a rate of 25 per minute. There was no venous distention and the peripheral pulses were equal without paradoxical pulsation. The chest was symmetrical, with dullness and bronchial breathing at the left base posteriorly, suggesting an accumulation of fluid. The heart was enlarged 2.0 cm to the left of the midclavicular line. There was a grade 4, harsh, to-and-fro pericardial friction rub along the left sternal border and extending from the pulmonic to the xiphoid area. There was no edema. The venous pressure was 180 mm of water.

The serial electrocardiographic findings between the sixth and twentieth days of the illness were compatible with those of acute pericarditis. The T waves became flat in leads 1 and aVF; diphasic in leads 2 and V_5; and inverted in leads 3 and V_1 through V_4. These changes were associated with slight elevation of the ST segments in V_2 and V_3.

A roentgenogram on the sixth day of the illness revealed cardiac enlargement with a small amount of fluid in the left pleural cavity. Serial roentgenograms between the sixth and twenty-first hospital days showed an increasing amount of fluid in the left pleural cavity with a decrease in size of the cardiac silhouette.

The laboratory examination demonstrated a white blood cell count of 15,350, with 88 per cent polymorphonuclear leukocytes. The hemoglobin was 9.9 Gm per 100 ml, the hematocrit 29 per cent, and the VDRL was negative. The SGO-T level on two occasions was 10 units and less. The heterophil agglutination, cold agglutinins, and L.E. cell preparations were negative. The corrected erythrocyte sedimentation rate (Wintrobe method) was 30 mm in one hour. The C-reactive protein was 3+, and the antistreptolysin–0 titers were 250 and 166 Todd units. Blood, cervical, and pharyngeal cultures were negative for pathogens.

Thoracentesis of the left chest on the eighth day of illness and again on the tenth day produced 60 cc and 250 cc, respectively, of straw-colored fluid with specific gravity of 1.017 and white cell count of 3,600, with 59 per cent polymorphonuclear leukocytes, 41 per cent lymphocytes, and 3 per cent unidentifiable cells. The total protein content of the fluid was 3.6 Gm per 100 ml.

Bacterial smears, cultures, and cell blocks were

TABLE II

Serial Influenzal Hemagglutination Inhibition Antibody Titers

Case No.	Type A (Japanese)				Type A (Denver)				Type B (Great Lakes)			
	Acute phase (1–4 weeks)		Convalescent (4–12 weeks)		Acute phase (1–4 weeks)		Convalescent (4–12 weeks)		Acute phase (1–4 weeks)		Convalescent (4–12 weeks)	
1 (B. K.)	<1:5	1:10	<1:5	<1:5	<1:5	1:10	<1:5	<1:5	**1:30**[a]	**1:160**	**1:80**	**1:20**
2 (H. G.)	*<1:5*[b]	*1:30*	*1:15*	*<1:10*	<1:5	<1:10	<1:10	<1:10	**1:20**	**1:80**	**1:180**	**1:20**
3 (G. M.)	<1:10	<1:10	<1:10	—	<1:10	<1:10	<1:10	—	**<1:10**	**1:40**	**1:15**	—
4 (A. B.)	—	<1:10	<1:10	<1:10	—	<1:10	<1:10	<1:10	—	**1:40**	**1:40**	**1:40**
5 (R. T.)	*<1:5*	*1:10*	*1:20*	*1:30*	<1:10	1:20	1:15	<1:10	**<1:10**	**1:240**	**1:320**	**<1:10**
6 (R. N.)	**<1:160**	**1:320**	**1:640**	**1:640**	<1:10	<1:10	<1:10	<1:10	1:20	1:20	1:20	1:40
7 (E. C.)	—	—	<1:5	<1:5	—	—	<1:5	<1:5	—	—	*1:10*	*1:10*
8 (P. H.)	**<1:10**	**1:40**	**1:80**	**1:20**	1:20	1:40	1:40	1:20	1:15	1:10	1:10	1:10

[a] **Bold face** numbers = significant antibody titers compatible with infection by the influenza virus.
[b] *Italic* numbers = possible significant antibody titers.

negative. Histoplasmin and tuberculin skin tests also were negative. Influenza titers taken at approximately two-week intervals are shown in Table II.

Clinical Course: While in the hospital the patient continued to complain of substernal pain, although the temperature, pulse, and respirations returned to normal within 24 hours. The pericardial friction rub persisted for 10 days, and the chest pain progressively improved. On October 10, 1957, 23 days after the illness began, the patient was discharged from the hospital without cardiovascular symptoms and without signs of a pericardial friction rub.

Second Hospitalization: On October 14, 1957, while playing with her child, the patient experienced sudden sharp substernal pain radiating through to the back, associated with marked anxiety and dyspnea. The patient was again hospitalized. On physical examination the temperature was 98.4°F, respirations 20, pulse 100, and blood pressure 130/90. A rough to-and-fro pericardial friction rub was localized at the fourth and fifth interspaces just to the left of the sternum. The peripheral pulses were equal, and there was no paradoxical pulsation. Serial electrocardiograms during the next 16 days again displayed minor ST segment and T wave changes suggestive of subacute pericarditis. Serial roentgenograms revealed no cardiac enlargement, and the lung fields remained clear. The routine laboratory examinations, including liver-function studies, heterophil agglutinations, cold agglutinins, and blood cultures, were normal.

The patient was given prednisolone with prompt relief of pain and dyspnea. Prednisolone was continued for 10 days during this hospitalization with a progressive reduction in dosage. The friction rub disappeared on the tenth day, and the steroid medication was discontinued. There was no evidence of pericardial effusion, paradoxical pulsation, or myocardial insufficiency. The patient was discharged on the twenty-eighth hospital day, and for six months there was intermittent recurrence of chest pain; however, for the past two months she has been without symptoms.

Comment: It is of interest that the pericarditis occurred at the time of delivery and during the postpartal period. For many years, instances of "postpartal" heart disease have been reported[33,50–58] without a previous history or clinical findings of heart disease. In fatal cases, the myocardium has shown moderate infiltration of lymphocytes and macrophages. In 1954, Bashour and Winchell[58] reported two patients with "postpartal heart disease." One case appeared to have had a hypersensitive reaction to sulfanilamide and in the other influenza type virus A was considered the etiologic agent. In 1958, Silber[33] reported four patients with viral myocarditis as instances of "postpartal myocarditis." One was associated with the primary atypical pneumonia virus, and one with mixed influenza A and B infection. The other two patients were assumed to have a pericarditis of viral origin. All these patients had excellent recoveries. As emphasized by Silber,[33] "postpartal heart disease" is probably not due to a specific entity or even necessarily related to pregnancy or the puerperium, but may be related to one of a number of different etiologic agents. It appears that all such instances of "postpartal heart disease" should be suspected of being myopericarditis of viral etiology.

CASE 2. H. G., a 48-year-old white male engineer, entered St. Thomas Hospital on January 24, 1958, with the chief complaint of "severe chest pain" extending to both arms, of three hours' duration. Ten days prior to admission the patient had a "bad cold" with generalized muscle aching and fever. These symptoms disappeared in three days, but nasal congestion, cough, and generalized fatigue were present at the time of admission to the hospital.

The patient's history revealed that in 1953 he had had a cholecystectomy; in March, 1957, he experienced an acute anterior-lateral myocardial infarction; and in June, 1957, an acute inferior myocardial infarction. On October 16, 1957, he received 0.1 cc of influenza vaccine (type A) intradermally.

On examination, the temperature was 99.4°F, pulse 70, respirations 20, and blood pressure 90/60. The patient was dyspneic and orthopneic. There was moderate venous distention of the jugular veins with the patient in semiupright position. The left cardiac border was 2.0 cm to the left of the midclavicular line and the heart sounds were of poor quality. A grade 4, harsh, rough, to-and-fro friction rub was audible over the fourth and fifth interspaces to the left of the sternal border. The radial pulses were weak, but no paradoxical pulses were found. Fine, moist rales were audible over the left lung base posteriorly and laterally.

Serial electrocardiograms from the day of admission to the twentieth day of illness demonstrated a slight elevation of the ST segments in leads 1, 2, and V_1 through V_6, with later inversion of the T waves in leads 1, 2, 3, aVF, V_1 through V_6, and an isoelectric T wave in aVL. These ST segment and T wave changes were compatible with acute pericarditis superimposed on patterns of previous anterior and inferior myocardial infarctions.

A roentgenogram on the second hospital day showed moderate left ventricular enlargement, and minimal linear atelectasis at both lung bases. On the nineteenth day there was a small amount of pleural effusion in the left chest, but the lung fields remained clear.

The laboratory determinations revealed the initial white blood cell count to be 9,100 with a normal differential. The SGO-T levels were 14, 74, 66, and 19 units on

the first four days of hospitalization, respectively. The serum cholesterol level was 270 mg per 100 ml. The ESR was 36 mm. The CRP was 4+, and the ASO titer was 50 Todd units. The VDRL, heterophil agglutination, cold agglutinins, and agglutinations for typhoid, brucellosis, and tularemia were negative. The sputum and blood cultures were negative for pathogens. The sequential influenza titers are shown in Table II.

Clinical Course: On the third hospital day, the patient developed a temperature of 101°F, a protodiastolic gallop rhythm, and clinical evidence of myocardial insufficiency. After digitalization, he was given oxytetracycline 250 mg every four hours for a left lower lobe pneumonitis. The friction rub disappeared after seven days and the protodiastolic gallop rhythm disappeared after eight days. On the twentieth hospital day, the patient developed an acute psychosis with hallucinations, agitation, and bizarre behavior. After three weeks of psychiatric observation, this disturbance disappeared and he returned to work, approximately two months after the onset of the acute illness. There has been no recurrence of symptoms for the past seven months.

Comment: This patient presented difficult diagnostic problems. He had experienced two previous myocardial infarctions which complicated the diagnosis of pericarditis, and the finding of an elevated SGO-T level tended to substantiate the diagnosis of still another myocardial infarction. However, two instances of acute "nonspecific" pericarditis with elevated SGO-T levels of 75 and 52 units, respectively, have been reported,[59] and the present author has reported[60] a case of acute pericarditis due to tularemia, with an elevated SGO-T of 80 units. These examples and the plausibility of epicardial inflammation as a cause of transaminase liberation suggest that this measurement will not discriminate between infarction and pericarditis. The possibility of acute pericarditis was suggested by the onset of "la grippe" ten days prior to the acute episode, the presence of the pericardial friction rub at the onset of the substernal pain, the nonspecific electrocardiographic changes, the response of the influenzal antibody titers, and the subsequent clinical course.

CASE 3. G. M., a 43-year-old white male, entered St. Thomas Hospital on March 11, 1958, with the chief complaint of "chest pain spreading to the left shoulder" of two weeks' duration. Three weeks prior to admission, i.e. one week prior to the present illness, the patient had "influenza" characterized by "fever, severe headache, generalized aching, and fatigue." One week later, he developed the presenting symptoms. The pain was described as "squeezing," constant, dull, and it was aggravated by breathing and swallowing. The patient had not received influenza vaccine.

On examination the temperature was 99.6°F, the pulse 100, respirations 20, and blood pressure 163/100. There was no venous distention and the lung fields were clear. The heart was not enlarged, and there was a normal sinus rhythm. A grade 1, rough, to-and-fro pericardial friction rub extended from the four to the sixth interspace along the left sternal margin. The peripheral pulses were equal and there was no paradoxical pulsation.

Serial electrocardiograms between the sixth and sixteenth hospital days showed progressive flattening and inversion of the T waves in leads 1, 2, 3, aVL, aVF, and V_4 through V_6. By the thirty-sixth day, the electrocardiogram had returned to normal.

A roentgenogram revealed no cardiac enlargement and clear lung fields.

On laboratory examination the white blood cell count was 7,000 with a normal differential. The ESR was 9 mm. The SGO-T was 17, 27, and 24 units on the first three successive hospital days. The VDRL, CRP, cold agglutinins, and heterophil agglutination were negative. The ASO titer was 12 Todd units, and the throat and blood cultures were negative for pathogens. The influenzal antibody titers are shown in Table II.

Subsequent Course: The pericardial friction rub disappeared in 48 hours, and the temperature returned to normal in three days. After six days the patient was without pain, and he was discharged on the tenth day. There has been no recurrence of cardiovascular symptoms in the ensuing six months.

CASE 4. A. B., a 59-year-old Negro male, was seen on February 22, 1958, with the chief complaint of "severe chest pain moving down the left arm" of three days' duration. Two weeks earlier, he had an acute episode of "flu" characterized by headaches, fever, cough, and generalized malaise. Eleven days after this cleared, i.e. three days before admission, a severe, constant, "constricting" substernal pain radiating to the left arm appeared which was aggravated by coughing, swallowing, and exertion.

The patient's history revealed that in 1934 he had syphilis and gonorrhea, which yielded to two years' treatment. He had not received influenza vaccine.

On physical examination the temperature was 99°F, pulse 75, respirations 20, and blood pressure 140/80. The radial pulses were equal, and there was no paradoxical pulsation. The chest was clear and the heart was not enlarged, but the heart sounds were of poor quality. There was a grade 1, rough, to-and-fro pericardial friction rub along the left sternal border extending from the fourth to the sixth left interspace.

Serial electrocardiograms between the first and thirty-second hospital days revealed that an incomplete A-V block with a PR interval of 0.24 second was present initially, and there was slight elevation of the ST

segments in leads 1, 2, aVL, aVF, and V_2 through V_6. The electrocardiogram had returned to normal with a PR interval of 0.19 second 57 days after the illness began.

A roentgenogram showed that the heart was not enlarged and the lung fields were clear.

Laboratory examination revealed the white blood cell count to be 8,600 with a normal differential. The ESR was 27 mm in one hour, and the SGO-T determinations were 72 and 42 units on the first and second hospital days, respectively. The VDRL, CRP, ASO titers, heterophil agglutination, and liver-function studies were normal. Influenzal antibody titers taken at approximately two- to three-week intervals are shown in Table II.

Subsequent Course: The patient was treated at home, and after three days the chest pain subsided. The temperature returned to normal and the pericardial rub disappeared, but during the next seven weeks the substernal pain often recurred with exertion. For the past four months there has been no recurrence of symptoms.

Comment: It is of interest that this patient developed an incomplete A-V block associated with the pericarditis. The literature indicates that disturbances of conduction are not unusual in cases of heart involvement due to influenza.[61–72]

CASE 5. R. T., a 42-year-old white male, entered Vanderbilt University Hospital on January 26, 1958, with the chief complaint of "severe chest pain" of 24 hours' duration. The day prior to admission, while hunting rabbits, he developed substernal "aching" pain which did not radiate nor was the pain accentuated by deep breathing. The pain became more intense, and was associated with shortness of breath. That evening a "shaking chill" developed, and the pain became accentuated by lying on the side or the stomach, or by swallowing, but was relieved by lying on the back.

The patient described an episode of "pleurisy" 36 years before. He had not received influenza vaccine.

On examination the temperature was 99.8°F, pulse 75, respirations 26, and blood pressure 140/80. There was slight venous distention when the patient was sitting at a 45° angle. The left cardiac border was 10.0 cm from the midsternal line in the fourth interspace. A grade 4, rough, to-and-fro pericardial friction rub was clearly audible over the fourth to the sixth interspace, and the sound was intensified by leaning forward. The first apical sound was obliterated, but the pulmonic and aortic components of the second sound were normal over the base of the heart. The lung fields were clear, and there was no paradoxical pulse.

Serial electrocardiograms between the first and sixteenth days of illness revealed a sinus arrhythmia with a rate of about 90 per minute. The PR interval was 0.20 second, and the QRS interval 0.08 second. The

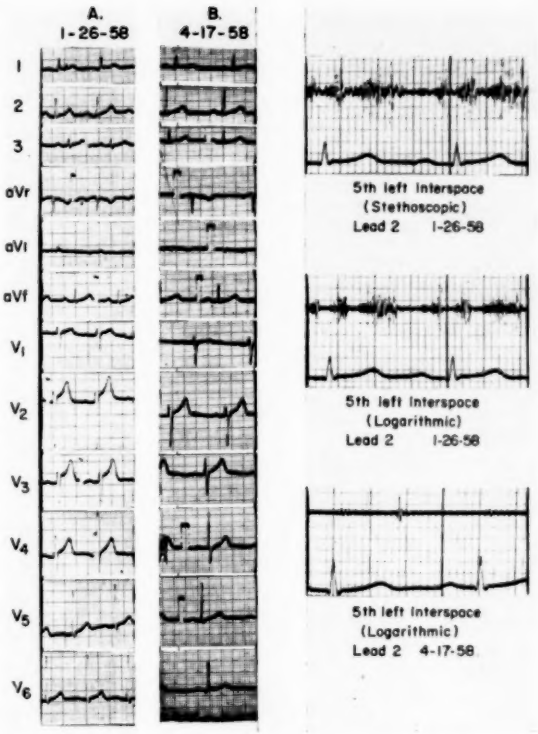

FIG. 1. Case 5. The electrocardiogram on January 26, 1958, demonstrates ST segment elevation without T wave inversion. This change is correlated with the high-frequency vibrations seen on the phonocardiogram due to the pericardial friction rub. By the twenty-second day both the electrocardiogram and the phonocardiogram had returned to normal.

ST segments were slightly elevated in leads 1, 2, aVL, aVF, V_1 through V_6, and the T waves became lower in voltage. These serial changes were suggestive of acute pericarditis (Fig. 1).

A phonocardiogram on the day of admission demonstrated the rub during atrial and ventricular systole fusing with the first and second sounds (see Fig. 1). By the twenty-second day, the phonocardiogram and electrocardiogram had returned to normal.

A roentgenogram demonstrated blunting of the right costophrenic angle; otherwise, the heart and lung fields were normal.

Laboratory examination revealed the white blood cell count to be 8,200, with 69 per cent polymorphonuclear leukocytes, 19 per cent lymphocytes, 4 per cent atypical lymphocytes, and 8 per cent monocytes. The red blood cell measurements were normal. The ESR was 6 mm, the CRP 3+, and the ASO titer less than 50 Todd units. The VDRL, and serial cold agglutinins, heterophil agglutinations, and agglutinations for tularemia, brucellosis, and typhoid fever were negative. The tuberculin skin test (1:1000) after 48 hours developed 7 mm of induration. This was interpreted as positive. Influenzal antibody titers

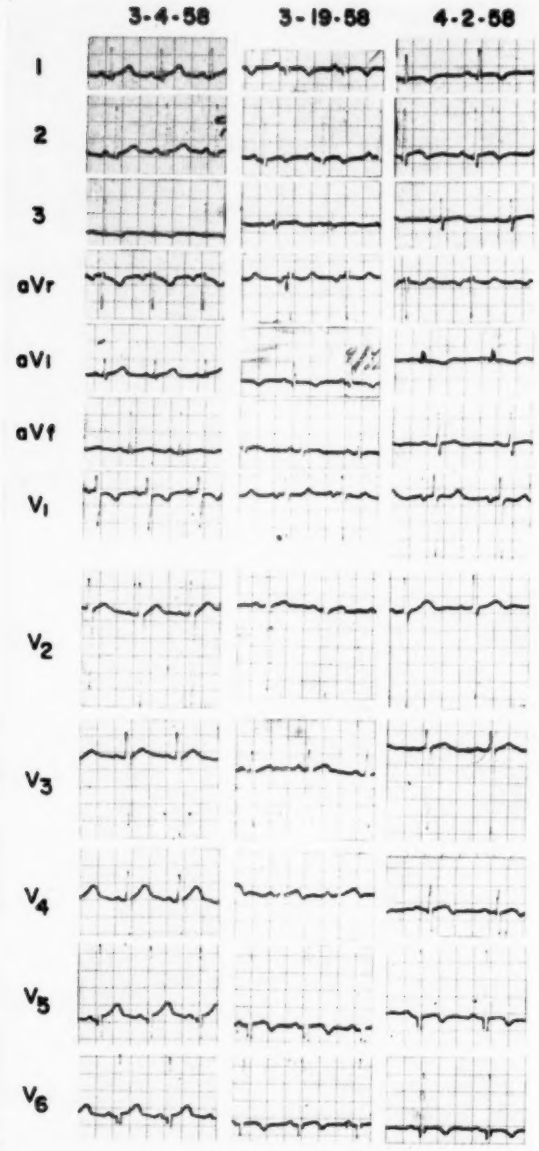

FIG. 2. Case 6. The serial electrocardiograms show early generalized ST segment changes with later T wave inversion characteristic of acute pericarditis.

taken at approximately two- to three-week intervals are shown in Table II.

Subsequent Course: While the patient was in the hospital, the pericardial friction rub gradually diminished in intensity and disappeared by the seventh day. He was discharged four days later, returned to work, and has been without recurrence of symptoms for the past seven months.

CASE 6 (presented by permission of Dr. William Ewers). R. N., a 31-year-old white male, entered Vanderbilt University Hospital on March 2, 1958, with the chief complaint of "generalized aching, chest pain, and fever" of six days' duration. The patient had been in good health until six days prior to admission, when he suddenly developed a severe substernal pain which was aggravated by leaning forward, but little affected by respiration. On the following day, he experienced generalized malaise associated with a severe headache and neck pain. Three days later, he developed a temperature of 101°F and a cough productive of small amount of "blood-streaked" sputum. On the following day, a roentgenogram was interpreted as showing "bronchopneumonia," and the patient was hospitalized.

At age ten, the patient had an appendectomy which was complicated by pneumonia. He had not received influenza vaccine.

On physical examination the temperature was 101°F, pulse 108, respirations 26, and blood pressure 135/70. There was an erythema of the posterior pharyngeal wall. The chest was symmetrical and there were fine, moist, crepitant rales over both lung bases posteriorly. The heart was not enlarged to percussion. There was a sinus tachycardia with a rate of 108 per minute. The heart sounds were of good quality, and there was an accentuation of the aortic component of the second sound. On the following day, a grade 2, rough, to-and-fro pericardial friction rub was heard along the left sternal border from the third to the fifth interspace, and the heart was enlarged 3.0 cm to the left of the midclavicular line. There was a definite paradoxical pulse of 6 mm Hg.

Serial electrocardiograms taken between the second and thirty-first hospital days revealed a sinus tachycardia at a rate of 104 per minute. The PR interval was 0.14 second, the QRS interval 0.07 second, and the QT interval 0.31 second. The axis was normal. The ST segments were slightly elevated in leads 1, 2, aVL, and V_4 through V_6, and slightly depressed in leads 3, aVR, and V_1. The successive electrocardiograms (Fig. 2) showed ST segment elevation and T wave inversion suggestive of acute pericarditis. On the fourth hospital day the patient had several episodes of paroxysmal atrial fibrillation with a ventricular rate of approximately 180 per minute. These episodes recurred during 24 hours and then subsided spontaneously.

A roentgenogram on the second hospital day revealed that the cardiac silhouette had increased markedly in size. The enlargement was generalized and suggested pericardial effusion. Two days later, fluoroscopy showed further increase in heart size, and the pulsations were feeble or absent over both ventricular areas. On the tenth hospital day a pleural effusion developed at the left base. By the thirty-first day the cardiac silhouette had returned to normal (Fig. 3).

On laboratory examination the white blood cell count was 5,500. The differential demonstrated 20 per cent juvenile cells, 43 per cent polymorphonuclear leukocytes, 17 per cent lymphocytes, 12 per cent atypical lymphocytes, 7 per cent monocytes, and 1 per cent

FIG. 3. Case 6. The successive roentgenograms demonstrate the development of pericardial effusion and/or myocardial dilatation due to active myocarditis. By the thirty-first day, the roentgenogram had returned to normal.

eosinophils. The red blood elements and urine analysis were normal. The ESR was 43 mm. The ASO titer was 150 Todd units, and the CRP was 3+. SGO-T determinations on the first and second hospital days were 23 and 67 units. The L.E. cell preparation, febrile agglutination, VDRL, liver-function studies, heterophil agglutination, and agglutinations for tularemia, brucellosis, and typhoid fever were normal. Blood cultures were negative for pathogens and the tuberculin skin test was negative. After 48 hours, the histoplasmin skin test (1:100) was interpreted as border-line. Influenzal antibody titers are shown in Table II.

Subsequent Course: While in the hospital, the patient was treated with 250 mg tetracycline every six hours for 21 days. The temperature varied from 103.2°F to 99°F for two weeks, and then returned to normal the following week. The venous pressure was 15.1 cm and the circulation time (arm-to-tongue with Decholin) was 23 seconds on the third hospital day. The pericardial friction rub disappeared after two weeks and the patient was discharged on the twenty-first day. For the next eight weeks there was occasional recurrence of chest pain, but for the past two months there have been no cardiovascular symptoms.

CASE 7. E. C., a 38-year-old white male factory worker, was seen on April 18, 1958, with the chief complaint of "chest pain" of six weeks' duration. Two months prior to admission, the patient had "influenza," and two weeks following the influenza he developed a dull "aching" substernal pain which lasted for approximately two hours at a time associated with "shortness of breath." The pain was aggravated by exercise and radiated to the left precordium.

The patient's past history revealed that in 1947 he had primary syphilis. He was treated with penicillin, and the serologic tests have remained negative. The patient received 0.5 cc of type A influenza vaccine subcutaneously in October, 1957.

On examination weight was 220 lb, temperature 99°F, pulse 88, blood pressure 130/80, and respirations 20. The patient complained of moderate substernal pain during the examination. The heart was not enlarged, but the heart sounds were of poor intensity and there was a grade 1, rough, to-and-fro pericardial friction rub over the fourth and fifth interspaces just to the left of the sternum. The lung fields were clear, and there was no paradoxical pulse.

Serial electrocardiograms between the second and eighteenth days revealed low voltage QRS of 0.45 mv, flat T waves in leads 1, 2, 3, aVR, aVL, aVF, and inverted T waves in V_4 through V_6.

On fluoroscopy there were normal ventricular pulsations and no evidence of cardiac enlargement. The lung fields were clear.

On laboratory examination the white cell count was 6,600 with a normal differential. The ESR was 12 mm in one hour. The SGO-T levels were 14 and 10 units on the first and second hospital days. Influenzal antibody titers taken at approximately two-week intervals are shown in Table II.

Clinical Course: While at rest, the pericardial friction rub disappeared in four days, but for four weeks the patient continued to complain of recurrent substernal pain on exertion. The electrocardiogram returned to normal within three weeks, and the patient returned to work and has been asymptomatic for six months.

Comment: Unfortunately, an influenzal titer was not taken at the onset of "influenza." Although it is possible that the "nonspecific" pericarditis was not associated with the influenza, the finding of a positive titer two months later is strongly suggestive that the patient had type B (Great Lakes) influenza. From the history the "nonspecific" pericarditis was associated with the influenzal infection.

CASE 8. P. H., a 15-year-old white farm boy, entered Vanderbilt University Hospital, on July 3, 1958, with the chief complaint of "fever and chest pain, associated with shortness of breath," of eight days' duration. Nine days prior to admission, the

patient awoke with "aching in the back" which radiated to the groin without other genitourinary symptoms. Four days later, because of persistent fever to 102°F, headaches, and sore throat, he was hospitalized.

The history revealed that at age nine the patient had acute rheumatic fever and was hospitalized for approximately one year. For the past six years, he had had dyspnea on physical exertion. He had not received penicillin in the past fourteen months, nor had he received influenza vaccine.

On physical examination the temperature was 104°F, pulse 112, respirations 30, and blood pressure was 160/0. There was a to-and-fro motion of the head synchronous with the cardiac cycle. There were pulsations of the retinal arterioles and veins, and a capillary pulsation was prominent in the nail beds. There was a disproportionate femoral systolic hypertension. Simultaneous blood pressure recordings in the legs were 280/0 and in the arms 180/0. There was a typical Duroziez's sign and Corrigan's radial pulse. There was slight stiffness of the neck with resistance to anterior flexion, and there was lateral nystagmus. The heart was enlarged to the anterior axillary line with the point of maximum impulse extremely active in the sixth interspace. There was a grade 2, rough, systolic murmur of maximal intensity over the aortic area which radiated over the precordium. There was a grade 4, decrescendo diastolic murmur of maximal intensity along the left sternal border, and a grade 2 diastolic murmur with a presystolic accentuation at the apex. The apical first sound was loud and snapping. The pulmonic second sound was accentuated. There was a positive Kernig's sign and an equivocal Brudzinski's sign.

A lumbar puncture revealed an opening pressure of 130 mm of water. The dynamics were normal, and 10 cc of clear fluid were removed without difficulty. The closing pressure was 80 mm of water. In the spinal fluid, there was a total of seven white blood cells present—five lymphocytes and two polymorphonuclear leukocytes. The total protein was 36 mg per 100 ml, and the sugar was 57 mg per 100 ml.

On laboratory examination the white blood cell count was 10,200, with a differential of 78 per cent leukocytes, 11 per cent lymphocytes, 10 per cent monocytes, and 1 per cent juveniles. The ESR was 32 mm in one hour. The urine concentrated to 1.018 with "ad lib" water intake, and there was a trace of protein in the urine. The blood sugar, NPN, electrolytes, liver-function studies, and VDRL were normal. Serial blood cultures were negative. SGO-T determinations on the first and second hospital day were 36 and 42 units. The latex fixation test was nonreactive, and the ASO titers at approximately two-week intervals were 166 Todd units. The CRP on admission was 3+. The venous pressures and circulation times remained normal. Influenzal antibody titers taken at approximately two-week intervals are shown in Table II.

The electrocardiogram on admission to the hospital demonstrated a sinus tachycardia at a rate of 100 per minute. The PR interval was 0.21 second, and the QRS interval was 0.08 second. The QT interval was 0.30 second. T wave and ST segment changes indicated left ventricular hypertrophy and strain, and the PR interval indicated an incomplete A-V block. Serial electrocardiograms between the sixth and fortieth hospital days revealed elevation of the ST segments in leads V_1 through V_6 with slight elevation of the ST segments in leads 1, 2, and 3, and inversion of the T waves in leads 1, 2, aVL, and aVF. The T wave was initially upright in aVR and the PR interval returned to 0.13 second within five days after admission. These serial electrocardiographic findings were indicative of acute pericarditis and myocarditis.

Fluoroscopy and roentgenograms demonstrated enlargement of the left atrium and both ventricles with normal vascularity of the lung fields. The transverse cardiac diameter was 17.3 cm and the transverse diameter of the chest was 29.5 cm.

Clinical Course: While in the hospital, the temperature remained elevated between 101°F and 103°F for four days with a persistent tachycardia at a rate of 120 per minute. Oral salicylate therapy was instituted. On the fourth hospital day, a presystolic gallop rhythm was audible associated with a grade 2, rough, to-and-fro pericardial friction rub of maximal intensity to the left of the sternum in the fifth and sixth interspaces. On the following day, the patient was started on 80 mg of prednisolone daily and within 24 hours the temperature returned to normal, and the friction rub and gallop rhythm rapidly disappeared. Because of the severity of this illness, prednisolone was continued for 53 days with a gradual reduction in dosage.

Comment: This case is of unusual interest. The onset of the present illness was not typical of acute recurrent rheumatic fever but was suggestive of a viral infection superimposed on inactive rheumatic heart disease. The ASO titers remained normal, and the influenzal antibody titers developed a greater than fourfold rise for type A (Japanese) influenza. The dramatic response of acute nonspecific and viral pericarditis to steroid therapy has been previously emphasized.[45,49,73,74]

Discussion

The etiology of acute benign "nonspecific" pericarditis is obscure.[13,14,24–40] Several cases of "nonspecific" pericarditis have recently been associated with the viral diseases.[33,41–43] Myocarditis, pneumonia, pleurisy, and pleural effusion frequently referred to as "complications"[7,13,20,37,75,76] of acute "nonspecific" pericarditis may be an integral part of a syndrome

which we would prefer to call *postviral myopericarditis*. Eight such cases of myopericarditis associated with a greater than fourfold rise in the influenzal viral antibody titer are presented.

As emphasized by Silber,[33] Kilbourne,[77] and Rhodes,[78] the demonstration of antibodies for a virus during the course of a disease does not necessarily constitute proof that the virus is the cause of the disease, though it is suggestive. On the other hand, the isolation of a virus having a temporal relationship to a disease does not prove that the virus is the etiologic agent. This observation was emphasized by Finland *et al.*[70]

Although it is well established that the influenzal viruses are causes of acute and chronic heart disease, the relationship between influenza and heart disease may be overlooked because of a time interval between the two disorders. After a review of the reported cases of influenza, from epidemic to epidemic,[61–72] it is of interest to note that many of the cardiac complications of influenza occurred during convalescence and often after an apparent recovery from influenza.

The delayed "reaction" of myopericarditis suggests a hypersensitive mechanism to the viral infection. If this is the case, when the active infection has subsided steroid therapy would seem logical and should prove effective.

The clinical features of cardiac enlargement, gallop rhythm, and heart block associated with elevated SGO-T determinations indicated myocarditis in half of these patients. The leukocytosis that often accompanies "nonspecific" pericarditis may be a reflection of an associated myocarditis similar to the leukocytosis found with an acute myocardial infarction.

The symptoms of acute "nonspecific" pericarditis must often lead to an erroneous diagnosis of myocardial infarction. Since patients with the former usually survive and since they are often young, it is especially important that they should not be stigmatized by such an error. Close attention to the serial electrocardiographic pattern is important. The fibrinogen polymerization test described by Fremont *et al.*[79] may prove of value in differentiating acute pericarditis from atypical myocardial infarction.

Summary

Eight cases of acute benign "idiopathic" or "nonspecific" pericarditis are reported in which an influenza virus was associated by history and serologic evidence with the acute pericarditis. The laboratory evidence demonstrated in five cases the type B (Great Lakes) influenza virus; in two cases both type A (Japanese) and type B viruses; and in one case the type A virus.

Seven of the eight patients reported were males. There was an interval of one or more weeks between the acute episode of "influenza" or "upper respiratory infection" and the cardiac disorder.

Acute "nonspecific" pericarditis is not necessarily "benign," as it is frequently associated with myocarditis, pericardial effusion, pleurisy, pleural effusion, and pneumonia. These features may be more appropriately designated as *acute myopericarditis*.

All patients with "postpartal heart disease," atypical myocardial infarction, or acute "nonspecific" pericarditis should be carefully evaluated for the recent presence of viral diseases as a possible cause of the cardiac difficulty. The hemagglutination inhibition influenzal antibody titer determinations, an ancillary service of the state laboratory, are recommended in all cases of acute "nonspecific" pericarditis in an effort to further classify these cases.

The history and the clinical and laboratory findings in these eight cases of "nonspecific" pericarditis suggest that this cardiac disorder is in fact a myopericarditis and the term *postviral myopericarditis* is suggested in preference to acute benign "nonspecific" or "idiopathic" pericarditis.

Addendum

Five additional instances of postviral myopericarditis associated with the influenza viruses have been observed. Of these adults, three were males and two were females. Compatible hemagglutination inhibition antibody titers were demonstrated for type A (Japanese) virus in one instance, type A (Denver) in two instances, type B in one instance, and both type A (Denver) and type B in one instance.

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Fatal Case of Acute Idiopathic Pericarditis

Discussion of the Character and Origin of Thoracic Pain in Acute Pericarditis *

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SINCE THE description of acute idiopathic pericarditis in 1942 by Barnes and Burchell[1] there have been numerous reports of the condition. The precise etiology of this form of pericarditis has remained obscure.[2] Descriptions of the disease have repeatedly stressed the occurrence of thoracic pain, often severe, and not infrequently in the sternal area. Indeed, this discomfort may resemble the pain of myocardial infarction or other vascular accident so as to cause clinical confusion, and it has led to the frequent designation of "pericarditis simulating myocardial infarction."[1,4,5] The mechanism of the painful symptoms occurring with acute serofibrinous pericarditis has been difficult to evaluate. The importance of pain was recently reemphasized to us in the clinical instance of acute pericarditis described here. In view of the diagnostic and therapeutic questions which were raised during these observations, an appraisal of the genesis of pericardial pain seems warranted.

REPORT OF A CASE

Clinical History: A 54-year-old male Negro was admitted to the Medical Service of the Homer G. Phillips Hospital on December 12, 1956, with the complaint of chest pain. The patient had considered himself in good health until three weeks before admission. At that time he noted pain in the lower substernal region which radiated to the upper thoracic area and neck. The pain was said not to radiate to the arms and hands. The discomfort was dull and constricting in quality. The patient continued to engage in heavy manual labor, loading trailer trucks, in spite of the pain. Three days prior to hospitalization the discomfort gradually increased in severity and became constant. One day before admission the pain became excruciating and was aggravated by deep respiration and by movements of the trunk. The sensation was confined to the anterior chest wall and substernal area and continued without radiation to the arms. The unremitting pain finally brought the patient to request treatment. The man had been generally healthy in the past. He had used alcohol over a long period and had taken moderate amounts before the onset of pain, and again two days previous to admission.

Physical Examination: The patient was a robust, normally developed Negro male. He exhibited marked apprehension. The temperature was 97.8°F, pulse 80 and regular, respiration 24, and blood pressure 80/60. Gross ocular and pupillary movements were normal, and the fundi were not notable. There was no evident venous distention. The heart was not enlarged, and no murmurs or friction rubs were discerned. The lungs exhibited no abnormal signs. The abdomen was mildly distended, and there was moderate tenderness to palpation in the right upper abdominal quadrant. The liver, spleen, and kidneys were not palpable. Bowel sounds were normal. The extremities were not notable and gross neurologic examination was negative.

Laboratory Data: White blood cells were 9,200 per cu mm with 12 per cent stab forms, 63 per cent polymorphonuclear cells, 22 per cent lymphocytes, and 3 per cent monocytes. Hematocrit and hemoglobin were 43 per cent and 13.2 Gm, respectively. The urine showed a trace of albumin. Serum diastase was 302 Somogyi units. The electrocardiogram (Fig. 1*A*) showed complete auriculoventricular dissociation, prominent Q waves in leads 3 and aVF, and elevated ST segments in leads 2, 3, aVF, V_5 and V_6. A second electrocardiogram 12 hours later (Fig. 1*B*) showed deeper Q waves and smaller R deflections in leads 3 and aVF, elevated ST segments in leads 1 and aVL, with persistent auriculoventricu-

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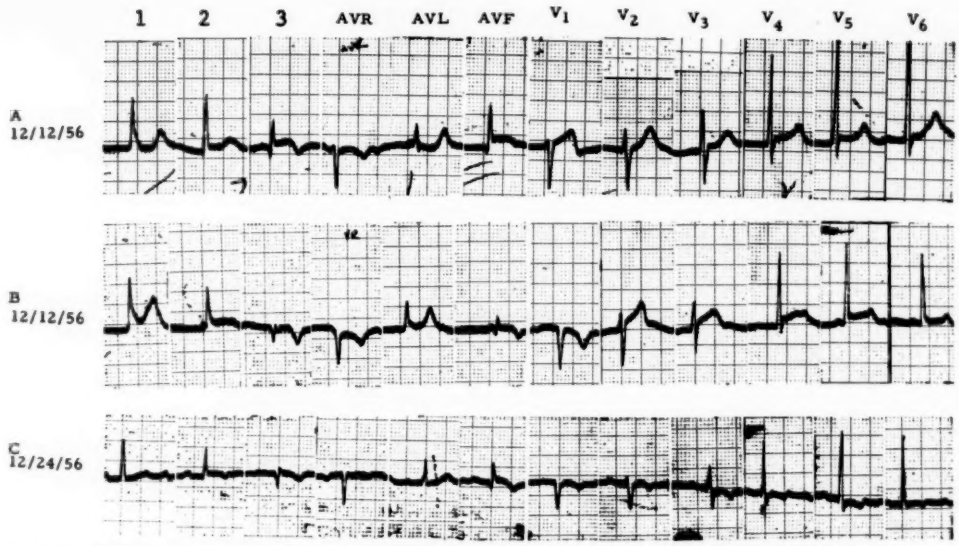

FIG. 1. Serial electrocardiographic tracings of this case of acute pericarditis. Note the prominent Q wave in leads 3 and aVF, suggesting myocardial infarction. Full description in text.

lar dissociation. An electrocardiographic diagnosis of acute pericarditis was considered; however, the signs were interpreted as more probably indicative of acute myocardial infarction.

Clinical Course: Because of the character of the pain and the electrocardiographic signs, a provisional diagnosis of myocardial infarction was made. Morphine was administered, oxygen was given by nasal catheter, and *l*-norepinephrine was infused to correct hypotension. The patient was moderately relieved, but he remained apprehensive until 75 mg of Demerol were given five hours after admission. The blood pressure rose to 130/80 and remained stable so that *l*-norepinephrine was discontinued within 24 hours. Anticoagulant therapy (Dicumarol) was begun on the first day and prothrombin times were maintained at approximately 25 per cent of normal. Roentgenologic examination of the chest was unsatisfactory because of severe illness; however, examination of the film showed possible elevation of the right diaphragmatic leaf.

In the following 10 days the patient seemed to improve, although mild shortness of breath continued. Serial electrocardiograms (Fig. 1*C*) showed a gradual return of ST segments to isoelectric level; there was flattening and later inversion of T waves in leads 2 and V_2–V_6 and the persistence of Q waves and inverted T waves in leads 3 and aVF. Within six days normal sinus rhythm had been re-established. Three days after admission a questionable double murmur at the apical area was described, and the heart sounds were thought to be distant. One observer interpreted the sign as a "to-and-fro" murmur. No friction sounds were recognized.

On the fourteenth day of hospitalization, the patient complained of dull pain in the left posterior hemithorax and there was dullness to percussion, decreased fremitus, and diminished breath sounds at the right lung base. A right thoracentesis was attempted, but the procedure was interrupted because of the sudden occurrence of weakness and dizziness. These symptoms were transient. Improvement continued until the eighteenth day of hospitalization, when the patient became acutely and severely dyspneic and exhibited marked apprehension. There was sinus tachycardia (130 per minute), and the electrocardiograms showed striking diminution of the QRS complexes in all leads without other significant change. The blood pressure was then 130/70. Demerol (100 mg) and oxygen were administered. Within a few hours the patient suffered marked respiratory distress and outspoken cyanosis. He complained bitterly of pain in the epigastrium with radiation to the right chest wall. The blood pressure fell to 90/60. Sinus tachycardia persisted.

Because of signs which were interpreted as massive right pleural effusion, a second thoracentesis was attempted. A 16-gauge needle was introduced into the seventh right interspace in the midaxillary line. No fluid was recovered and the procedure was promptly discontinued. In spite of continued administration of *l*-norepinephrine and oxygen, cyanosis and vascular collapse persisted and the patient died in severe dyspnea.

AUTOPSY EXAMINATION

Two needle puncture marks were noted in the seventh intercostal space in the midaxillary line of this normally developed Negro male. The important anatomic findings were in the thoracic and abdominal cavities. The pleural cavities did not contain excess

fluid. The lungs on section showed an edematous parenchyma.

The heart weighed 420 Gm. The pericardial cavity was partially obliterated by dense adhesions. The base and anterior portion were free and in these spaces 150 cc of dark bloody fluid (Hb 40 per cent Sahli) was contained. Adhesions separated with varying degrees of difficulty. Fibrin varying in density had formed in those areas not involved by adhesions. The myocardium was generally soft and flabby, softer in the portion adjacent to the epicardium; papillary muscles were also soft. The chambers were slightly dilated; the mural endocardium was dull; a few foci were even duller. Small atheromata were deposited on the aortic cusps. The coronary arteries showed occasional atheromata and an organizing thrombus was found in the midportion of the left coronary artery.

The peritoneal cavity contained 1,500 cc of dark blood (Hb 40 per cent Sahli). Further search for the source of this bleeding indicated well-formed clots, weighing 220 Gm, located between the dome of the liver and the inferior surface of the diaphragm, the dome of the right diaphragm being elevated to the level of the fifth rib on the right. The liver weighed 1,700 Gm. When the blood clots were removed, two needle tracts, 5 cm apart, were noted on the lateral surface of the hepatic dome. Section of the organ was brown with some lighter areas. These color changes did not follow any particular pattern. There was no increased fibrosis. The renal capsules stripped easily. There were no scars, and the renal vessels appeared normal. The other abdominal structures revealed no significant changes.

Microscopic Examination: The most arresting histologic pathology was noted in the heart. A dense coat of fibrin covered the epicardium, beneath which were scattered hemorrhagic areas (Fig. 2). Epicardial fat was moderate, but extended into the myocardium. Dense collections of inflammatory cells were found beneath the fibrin of the epicardium, and in some areas attempts at organization had begun. Small areas of necrosis with infiltrates of lymphocytes and macrophages were present at the outer edge of the myocardium and beginning loss of cellular outline could be seen here also. Elsewhere in the myocardium there were small areas of early necrosis. The endocardium was focally thickened. In one area of the left circumflex artery, thrombotic organization was noted. However, this organizing thrombus occluded the lumen only partially, and there was no evidence of infarction of the heart muscle in the area of this vessel.

The cytoplasm of the liver cells was generally less granular than normal and scattered cells were vacuolated. The tubular epithelium of the kidneys was swollen. Intimal hyperplasia of some of the smaller and medium-sized vessels was present. No lesions suggesting tuberculosis or other bacterial infection of the pericardium were discerned.

Discussion

The disease entity of acute idiopathic pericarditis has become familiar to clinicians. The general clinical course of the condition has been frequently described[1–20] and need not be repeated here. It is of importance, however, that this form of pericarditis usually appears following an upper respiratory infection, and may be heralded by the general symptoms of malaise, chills, and fever. Thoracic pain is often a dominant complaint, and gastrointestinal disturbances, with nausea and vomiting, are common. Pleuritis and pleural effusions have been encountered in a number of cases. There have also been some instances of shock, apparently resulting from the pericardial inflammation.[22] The occurrence of a pericardial friction rub is probably the most important sign of the disease, and it is present at some time during the course in the majority of patients with idiopathic pericarditis. Electrocardiographic patterns of pericarditis are also diagnostically significant, and, in the absence of a friction rub or other distinctive findings, may constitute the most reliable indication of the disease. The diagnosis of idiopathic pericarditis of course becomes final only when all other causes of pericarditis have been excluded.

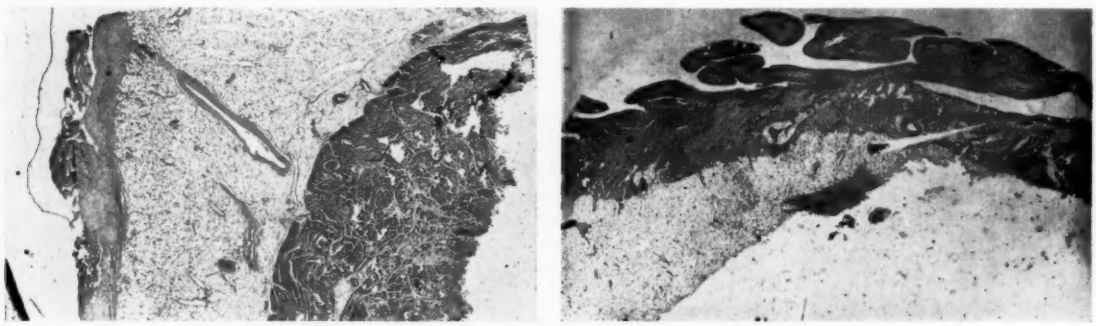

Fig. 2. Fibrin deposition within the pericardial space (see text).

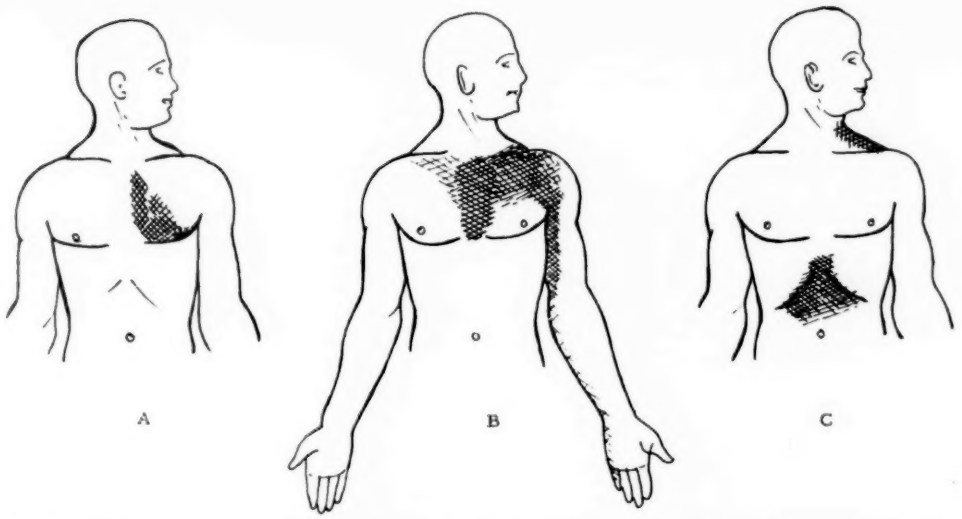

FIG. 3. Diagrammatic sketch of some of the common areas of pain perception in acute serofibrinous pericarditis. (*A*) and (*B*) illustrate by shading the precordial or substernal distribution of pain, with or without radiation to the shoulder and inner aspect of the arm and hand. Radiation of such pain may also involve the right shoulder and arm. The pain may be lancinating or mild; it may be perceived only on motion. The pain may be oppressive and constricting, and located in the substernal region, of many hours' duration. The latter discomfort is particularly reminiscent of myocardial infarction. Pericardial pain is occasionally perceived in the abdomen (*C*) or referred to the ridge of the trapezius muscle (see text).

Few of the reported cases of idiopathic pericarditis have terminated fatally. However, in the occasional necropsied cases[6–10] the lesions were characterized by a fibrinous exudate with dense fibrinous adhesions between the membranes, and by infiltration of the pericardial tissue with lymphocytes and granulocytes. Adjacent myocardial tissue frequently exhibited lymphocytic infiltrates in these cases. The causes of death were varied. In one patient[6] the pericardial space contained a large amount of blood; this patient had received anticoagulant therapy, and death was attributed to cardiac tamponade from the hemopericardium. In two instances, death was ascribed to the extensive inflammatory disease,[7,8] while in another case[9] a patient with healing pericarditis committed suicide, and at autopsy there was evidence of an organizing fibrinous process. Goyette[3] reported that pericardial biopsy in one of his cases of probable idiopathic pericarditis showed merely nonspecific inflammatory changes, with thickening of the membranes and infiltrations of small inflammatory cells into the deeper layers. The fundamental cause of the inflammatory process was not apparent in these cases on histologic or bacteriologic study, and the distinctly "idiopathic" character of the disease was amply confirmed.

In general, the pathologic changes observed in the heart of our patient were consistent with the lesions of nonspecific pericarditis, with extensive involvement of the pericardial membranes and the myocardium by the disease. In common with one of the autopsied cases of pericarditis, the pericardial sac of our patient contained bloody fluid. Nevertheless, the heart did not appear to be compressed by the fluid so that cardiac tamponade from fluid or frank blood was considered unlikely. The involvement of the pericardium and myocardium in the process appeared to be the direct cause of the heart failure and progressive clinical deterioration. Although a partially organized thrombus occupied the left circumflex coronary artery, the vessel was not occluded, and infarction of the corresponding myocardial wall was not present. Therefore, ischemia of the heart muscle could not be incriminated in the decline of cardiac function or as the cause of the pain. In addition, the cardiac disease was complicated by the accidental puncture of the liver from two attempted thoracenteses, and the accumulated blood between the hepatic dome and the diaphragm amounted to 220 Gm of clot. The hepatic wounds were small, and hemorrhage from them had stopped at the time of death.

From the clinical standpoint, the symptom of chest pain was strikingly prominent in this case,

and it closely resembled the pain of myocardial infarction. While the complaint of similar pain is a common feature of idiopathic pericarditis,[4-6] the discomfort is frequently not agonizing. The pain-sensitive portions of the pericardium have been considered so limited[21] that the origin of the discomfort occurring from pericardial disease has been difficult to evaluate. Therefore, a re-examination of our knowledge of the mechanisms of thoracic pain in general, and of pericardial pain in particular, is justified.

GENERAL ASPECTS OF PERICARDIAL PAIN

The intensity and location of pain in acute pericarditis may be variable. The symptoms have been variously described as dull and aching, sharp, lancinating, and oppressive. It may be so mild that the patient is aware only of vague thoracic distress, or it may be excruciatingly severe. The pain is frequently localized in the substernal or parasternal areas or in the precordium, and in some instances it radiates to the left scapular region, to the back, abdomen, left shoulder and arm, and commonly to the left side of the neck (Fig. 3). The onset of the symptoms is often gradual, but it may appear suddenly. When the onset of pain is precipitant, and particularly when it is subjectively appreciated as an *oppressive* or *constricting* thoracic discomfort, the symptoms may become suggestive of acute myocardial infarction or other vascular accident.

The well-known experiments of Capps and Coleman[21] have contributed to our knowledge of pain arising from the pleurae and pericardium. Their experiments indicated that the visceral pericardial membrane is quite insensitive to pain upon direct mechanical stimulation. On the other hand, the parietal pericardium appeared to be sensitive to pain from direct stimulation only in its inferolateral portion. The pain resulting from stimulation of the latter area was referred to the superior ridge of the homolateral trapezius muscle as sharply localized pain through the innervation of the parietal membrane by the phrenic nerve (Fig. 4). Therefore, on the basis of these observations, the sensory innervation of the pericardium is restricted to a small area. Capps and Coleman also showed that the parietal pleurae are sensitive to pain over the extent of the chest wall and periphery of the diaphragm through their innervation by the intercostal nerves. The visceral pleurae were found to be insensitive to direct mechanical stimulation. In common with the parietal pericardium, the sensory nerves of the central diaphragmatic pleurae are conveyed by the phrenic nerves.

Because of the acutely sharp quality of the pain of pericarditis in many cases and its location in the anterior chest region, the assumption has been made that it originates from a pleuritis that is contiguous with the pericardium. In addition, this pain may be accentuated on movement of the trunk and during paroxysms of coughing. These features also suggest that the pain results from inflammation of the neighboring membranes which are irritated and is also incited by these mechanical factors (sudden movement). Moreover, sharp pain in the epigastrium or along the costal margins may reflect a contiguous diaphragmatic pleuritis.

Conversely, the occurrence of substernal pain or "oppressive sensation" which occurs in many cases of acute pericarditis is less easily analyzed. In fact, the subjective resemblance of the pain to that of coronary disease may be so similar that it seems logical to consider the fundamental causes as closely related, or the same. If this is true, it

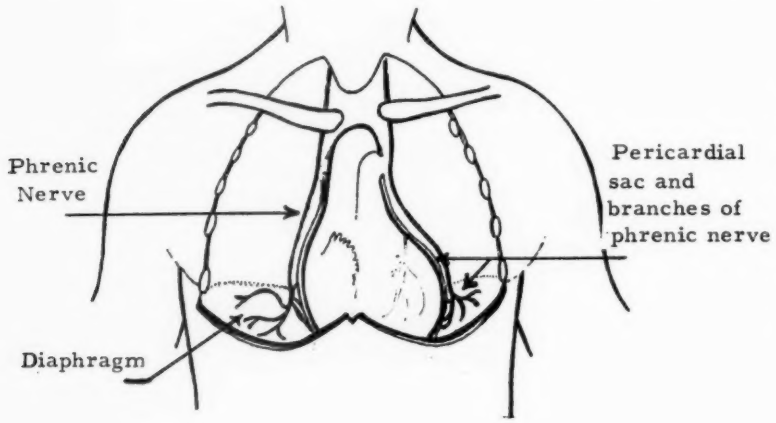

FIG. 4. Diagram of the distribution of sensory branches of the phrenic nerves to the central diaphragmatic pleurae and the inferolateral areas of the parietal pericardium. Sensory elements of the phrenic nerves also innervate the central diaphragmatic peritoneum. Pain arising in these areas is referred to the ridge of the homolateral trapezius muscle.

is possible that pericardial inflammation may invoke mechanisms of pain production through reflexogenic pathways that are common to various kinds of visceral disease. It will be necessary to consider briefly the origin of substernal pain that is characteristic of myocardial ischemia and of certain other disorders.

FACTORS PROVOKING SUBSTERNAL PAIN

It has been generally accepted that the immediate origin of cardiac pain arises from ischemia of the myocardium.[22] This concept has been based on correlative clinical and pathologic evidence of coronary insufficiency or frank coronary occlusion in patients with the peculiarly distressing discomfort which is characteristic of them. In addition, evidence has been adduced that ischemia of muscle in general (including the heart) permits the accumulation of metabolites[22] within the injured muscle which is the direct stimulus to pain nerve endings within the muscle tissue. Less apparent, however, is the actual source of the painful sensations. White[23] has stated that the heart is possessed of sparsely distributed sensory nerve endings that bear some histologic resemblance to sensory nerve endings in pain-sensitive tissues. He reasoned that an effective stimulus to the "cardiac pain nerve endings" originates in large areas of ischemia to provide spatial summation of impulses activating the nerve endings, thereby surmounting the sensory threshold. As an interesting corollary, White also pointed out that similar stimuli to pain occur in the bowel when it is forcibly distended. The sensation provoked by ischemic injury of the muscle is appreciated by the patient as an intensely unpleasant discomfort, usually in the substernal area, and variously described as "oppressive" or "constricting" or as a discomfort that is difficult to localize precisely.

Although pain may originate from nerve endings in the myocardium as described, the fact remains that certain thoracic visceral diseases other than diseases of the heart often provoke pain which is subjectively similar if not identical to cardiac pain itself. Therefore, other pain-producing mechanisms may be concerned. A logical viewpoint of the cause of substernal pain (from cardiac ischemia or other visceral disease) has been built upon the concept that the excitation of sensory receptors in injured visceral tissue stimulates reflex impulses that induce somatomotor effects as the direct source of pain. This phenomenon may be basically motivated by the entry of barrages of viscero-sensory nerve impulses into the spinal cord. These stimuli to the spinal cord then invoke motor nerve impulses and consequent contraction of distant muscle groups.[24] Wiggers[24] has suggested that sensory stimuli from an injured viscus (and particularly from the heart) result in sustained contraction of muscles of the thoracic cage. These muscle contractions, or "spasms," incite the thoracic (often substernal) pain.

This mechanism merits further attention. For example, it has been realized for many years that patients with osteoarthritis of the dorsal spine may have seizures of ill-defined, noxious sensation about the anterior chest wall and sternum from irritation of spinal nerves.[25] Similar painful symptoms may result from diaphragmatic hernia, esophageal inflammation, and occasionally from disease of the gallbladder and upper gastrointestinal tract.[26,27] In terms of pain, the common denominator of all of these disorders resides in the intensely disagreeable discomfort about the anterior chest. On the basis of these clinical facts, the fundamental causation of the symptoms, whether from heart disease or disease of other viscera, may involve muscular structures closely associated with the chest wall. The symptomatologic pattern further suggests that the internal intercostal muscles and perhaps the transversus thoracis muscles, by their position, may be concerned in reflexogenic contraction and resultant pain. Figure 5 shows the anatomic disposition of these muscles. The fibers of the two muscular groups embrace the anterior portion of the inner bony thorax, and because of the additional mass of the transversus thoracis, are concentrated in the sternal area. Sustained contraction and pain within these muscles could reasonably be expected to provoke the substernal discomfort that is characteristic of myocardial ischemia or of the other visceral diseases in question, including the occasionally distressing pain of acute pericarditis.

Although the pain of thoracic visceral disease, including pericardial pain, may be manifested by discomfort in the anterior chest (often substernal), the reference of the pain may likewise assume a similar pattern. The mechanism of referred pain is well known and need not be reviewed.[24] However, it is important that the viscera occupying the mediastinum are often possessed of visceral sensory nerve paths which find entry into the spinal nerves and cord at common levels. By these anatomic circumstances the discomfort arising from various diseases of the

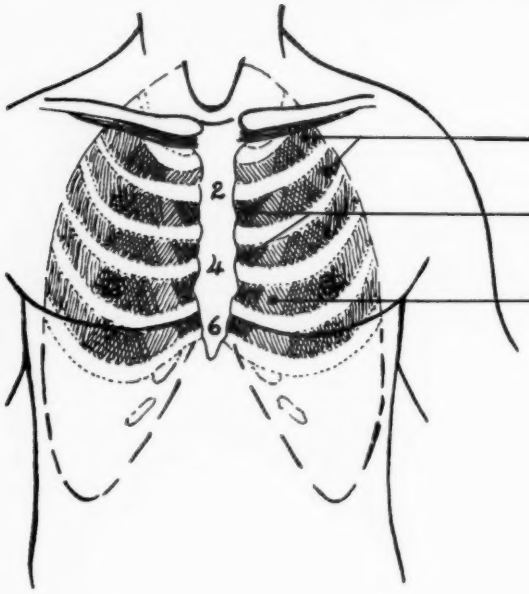

FIG. 5. Drawing of the general disposition of muscles of the anterior chest wall, which may give rise to pain through sustained contraction by reflex effects generated by tissue injury of intrathoracic organs. Sustained contraction of the internal intercostal and transversus thoracis muscles are assumed to be particularly important in the cause of substernal discomfort.

mediastinal organs may be referred to sites, such as to the left shoulder and arm, which are usually reserved for cardiac pain. By the same token, the pain of myocardial infarction, in some individuals, may be referred to the epigastrium or to the right upper quadrant, or even to the back and to the neck. Therefore, the reference of pain to various sites requires the same considered evaluation as does the dominant pain in each patient if clinical confusion of the diagnosis of pain source is to be avoided.

PERICARDITIS AND SUBSTERNAL PAIN

There have been frequent references to the symptom of substernal pain accompanying acute serofibrinous pericarditis.[1,3–6,14,15] In such instances, and in the case described here, the pain may not be characteristic of the irritation of serous surfaces, but rather of a more severe and highly noxious kind. As in the reported cases of idiopathic pericarditis, the inflammatory involvement of the myocardium (underlying the pericarditis) in our patient was definite although apparently not extensive, and seemed hardly sufficient to provoke pain of the duration and intensity observed. It seems logical to suggest that the painful symptoms arose by excitation of somatic pain nerve endings from stimulation of thoracic muscle contraction. In short, reflexogenic mechanisms may have been actuated by reflex stimuli resulting from damage to the pericardium and/or other structures forming the boundaries of the mediastinum.

When viewed from this standpoint, the occurrence of substernal or constricting chest pain in cases of acute pericarditis may be the signpost of a neurogenic somatic episode that could be similarly actuated by a variety of viscero-sensory impulses resulting from tissue injury or destruction. By similar means, tissue stimuli initiated by pericarditis (as well as by myocardial infarction in other cases) may possibly excite abdominal pain in occasional patients. Because of the variety of type and location of the painful symptoms of pericarditis, this entity should be considered in patients with anterior thoracic pain until the final diagnosis of the process causing the pain has been established.

SUMMARY

A 54-year-old man died with apparent acute idiopathic pericarditis. The clinical course of the disease was accompanied by agonizing substernal pain and terminated in congestive heart failure. The diagnosis of acute myocardial infarction was entertained. It is suggested that the substernal or peristernal pain from acute serofibrinous pericarditis, myocardial ischemia and infarction, diaphragmatic hernia, or other thoracic visceral disease may arise by similar mechanisms. It is further suggested that critical injury of the pericardial tissue may, in common with cardiac injury or injury to other organs, incite somatomotor reflexes resulting in sustained contraction of muscles of the anterior thoracic wall, accounting for the sternal pain or "oppression."

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Syndrome of Chronic Massive Pericardial Effusion

Report of a Case with an Associated Finding of Chronic Rheumatic Heart Disease

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MOST TEXTBOOKS of cardiology discuss acute cardiac tamponade or chronic pericarditis of the accretio or concretio variety, but little mention is given to chronic pericardial effusion.[1–4] While chronic pericardial effusions are known to occur in uremia and lupus erythematosus, for example, these effusions vary with the activity of the underlying disease and either disappear as the process becomes controlled or are part of a terminal episode. There is, however, a small group of patients in whom rather massive pericardial effusions have been observed to persist for many years. This group is not homogeneous, and although there are some clinical similarities in these patients, the associated pathologic and etiologic findings have been variable. There is no evidence that "viral idiopathic pericarditis" plays any role in the development of this syndrome.[5,6]

The discovery of still another patient with a chronic pericardial effusion is therefore worthy of comment.

CASE REPORT

G. S. M., a 33-year-old Negro woman, was seen for the first time in May, 1957, with complaints of mild exertional dyspnea and fatigue of about three months' duration. There were no other cardiac symptoms. She was able to complete a full day's work as a sewing-machine operator and take care of her home at night. She took no medication of any type. The remote past history was entirely negative, except for rare grand mal seizures which began in her teens. In 1949, after a seizure, she was told of some difficulty with her heart. In 1954, she was operated upon without difficulty for an ovarian cyst. The systemic review and family history were noncontributory.

Physical Examination: The patient was a well-developed, very tall female in no distress. Blood pressure was 120/80; pulse 80; respirations 18; temperature 98.6°F. Pulsus paradoxicus could not be elicited. The neck veins were flat and the hepatojugular reflux was negative. The PMI could not be palpated, but the area of cardiac dullness was displaced to the left. The apical first sound was loud, snapping, and accentuated. No systolic murmur was audible. After a normal second sound the opening snap of the mitral valve was heard, followed by a low-pitched rumbling murmur with presystolic accentuation. P_2 was accentuated and split. The lungs were clear. The liver was not palpable, and there were no peripheral evidences of congestive heart failure. The remainder of the physical examination was within normal limits.

Electrocardiogram: There was normal sinus rhythm with a P-R interval of 0.20 second. The P waves were enlarged and notched in standard leads 1 and 2 and were inverted in V_1. The QRS complexes in the standard and unipolar limb leads were of low voltage (Fig. 1). A vectorcardiogram taken with the cube system of electrode placement revealed a large triangular P loop which was posteriorly displaced in the horizontal projection and inferior and to the left in the frontal projection (Fig. 2). The QRS loop in the horizontal plane was inscribed in the usual manner, but was somewhat posteriorly displaced. The sagittal plane confirmed this. The QRS in the frontal plane was normal. The electrocardiogram and vectorcardiogram suggested the presence of pericardial effusion and enlargement of the left atrium.

Fluoroscopy: The heart was markedly enlarged to the right and left; there was an increased pulmonary artery segment, and pulsations of the cardiac borders were absent. No displacement of the barium-filled esophagus was observed. Chest roentgenograms corroborated the fluoroscopic findings (Fig. 3).

Additional Laboratory Data: The venous pressure was 15 cm of water with no rise on right upper quad-

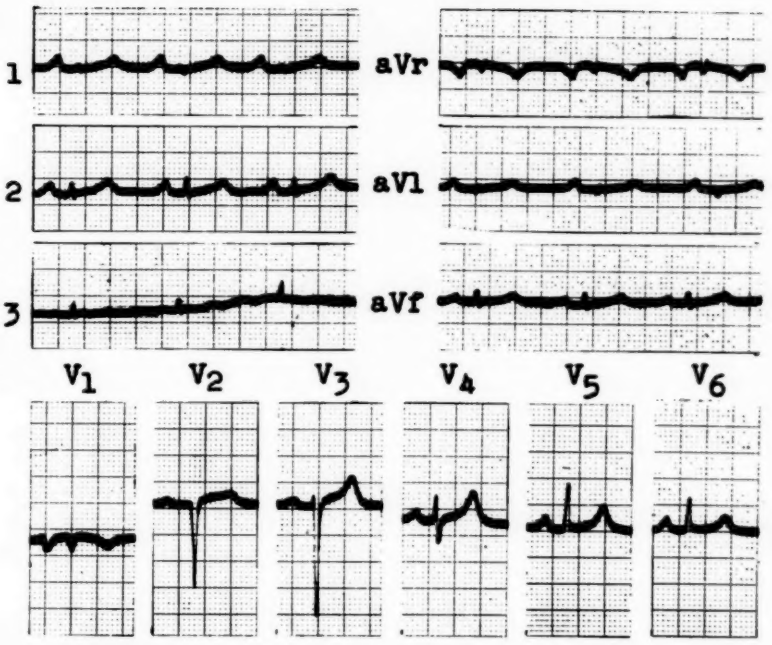

FIG. 1. Electrocardiogram showing regular sinus rhythm with a P-R interval of 0.20 sec. The P waves are large in the standard leads and large and inverted in lead V_1. The QRS is of extremely low voltage in the standard and unipolar leads.

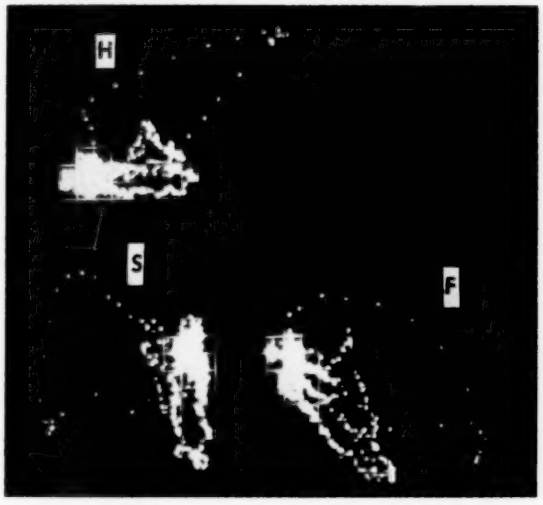

FIG. 2. Vectorcardiogram recorded with the cube system of electrode placement shows a large triangular P loop, which is posteriorly displaced (*H*) and directed inferiorly and to the left (*F*). The QRS loop is displaced posteriorly. (*H*, horizontal plane; *S*, sagittal plane; *F*, frontal plane.)

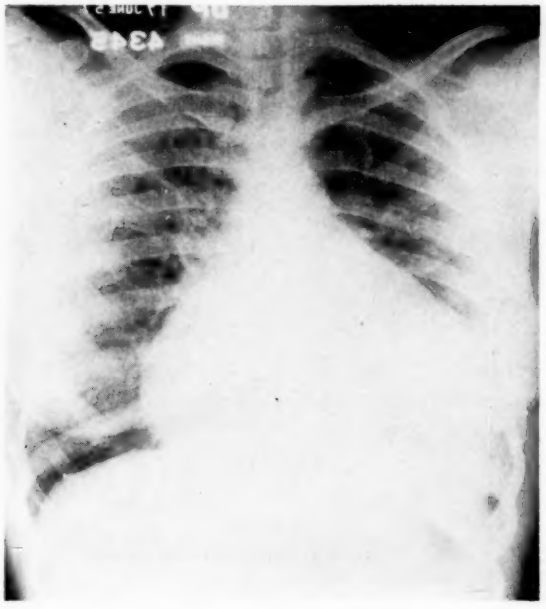

FIG. 3. Posteroanterior chest roentgenogram, taken on June 17, 1957, showing an extremely large cardiac silhouette to the right and left with fullness of the pulmonary artery segment.

rant pressure. The arm-to-tongue circulation time was 15 seconds (Decholin). The hemoglobin was 12.6 Gm per 100 ml, and the WBC was 8,400 with a normal differential. The sedimentation rate was 15 mm/hr (Westergren). A sickle-cell preparation was negative, as was the serologic test for syphilis. Complete urinalysis revealed no abnormality. The antistreptolysin titer was 126 units, protein-bound iodine 6.5 μg, and cholesterol 200 mg. Several lupus cell preparations were negative. The tuberculin test was negative in both strengths.

Clinical Impression: Chronic rheumatic heart disease plus a large pericardial effusion. The presence of the latter was difficult to explain on the basis of

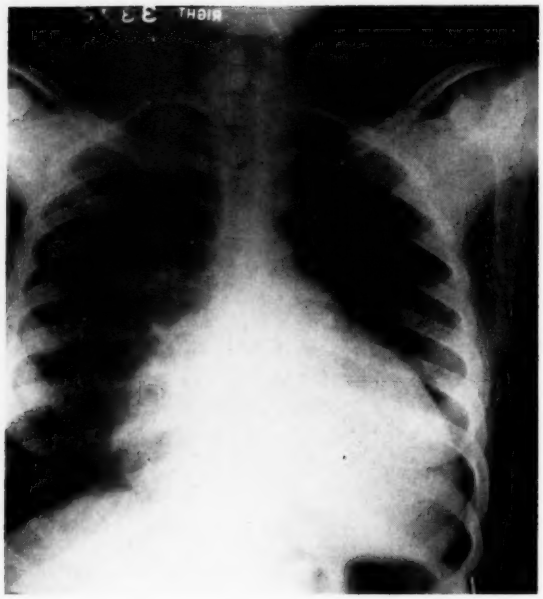

FIG. 4. Posteroanterior chest roentgenogram, taken on June 24, 1954, showing the same cardiac size and contour as that present three years later.

congestive heart failure, rheumatic activity, or any other acute process, since there were no clinical or laboratory evidences to confirm them. About this time a chest roentgenogram was discovered which had been taken three years previously in a routine preoperative survey. This film looked exactly like the one taken during the present investigation (Fig. 4). Since the patient was almost entirely well during the three-year period from June, 1954, to June, 1957, and was under no medical therapy, these films gave conclusive evidence that the present effusion was of a chronic variety.

Cardiac Catheterization and Angiocardiography: The patient was admitted to the Newark Beth Israel Hospital and right-sided cardiac catheterization was performed. No abnormalities were discovered. The intracavitary pressures and oxygen contents were normal, as well as the cardiac output at rest and after exercise. An angiocardiogram revealed the cardiac chambers to be of slightly increased volume, but in normal position. The outside thickness of the heart wall was markedly increased, which further corroborated the impression of pericardial effusion (Figs. 5 and 6).

Pericardiocentesis and Thoracotomy: In an attempt to distinguish the nature of the pericardial effusion, a pericardiocentesis was performed. Entry of the needle via the subxiphoid route was somewhat difficult, but a free flow of serous fluid was established. After withdrawal of about 30 ml of fluid, it was noted that the fluid became blood tinged. The flow stopped. The patient suddenly convulsed and went into shock. Emergency thoracotomy was performed, and a huge bloody pericardial effusion was evacuated. A rent in the right ventricular myocardium was discovered and repaired. However, the patient developed signs of cerebral injury due to anoxia and died 24 hours after the procedure.

POSTMORTEM EXAMINATION*

Gross Findings: The body was that of a tall, well-developed Negro female measuring 71 inches in length. There was a recently sutured curved surgical incision in the left anterolateral chest area.

Thoracic Cavity: The pericardium was wide open, having been previously incised and not sutured. It communicated with the left pleural cavity and with the incision in the intercostal space previously described. The right pleural cavity was largely obliterated by fibrous adhesions which enveloped the right upper lobe. There was no significant enlargement of the tracheobronchial or mediastinal lymph nodes.

Pericardium and Heart: The parietal pericardium was distinctly thickened throughout, measuring 1 mm. There was no hint of calcification, but its inner surface was slightly granular, injected, and opaque. There were no pericardial adhesions and, of course, at that time no pericardial fluid. The heart was large, weighing 475 Gm (expected weight, 299 $\pm$ 30 Gm[7]). The epicardium was smooth, but beneath it there could be seen an irregular but very extensive grayish, fibrous thickening, so that some of the normal landmarks of the exterior of the heart were effaced. There was a 1.5 cm oblique line of sutures on the anterolateral aspect of the right ventricle. The right atrium was considerably dilated and hypertrophied. The wall measured up to 0.6 cm. Its lining was thin, transparent, quite smooth, and lustrous. The tricuspid valve was normal. The right ventricle was dilated and the walls were thickened, measuring 0.9 cm. The pulmonic valve was normal. The pulmonary artery and its branches were somewhat dilated, but there was no hint of atherosclerosis. The left atrium was markedly dilated and hypertrophied, and the wall measured 0.8 cm. The endocardium was thickened and opaque. There were no thrombi.

The mitral valve was markedly stenotic, admitting less than $1^1/_2$ fingers. Its edge was markedly thickened and fibrotic, without evidence of calcification. The cusps were fused at their commissures. The chordae tendineae were thickened and shortened, and the papillary muscles were hypertrophied. There was a suggestion of a degree of insufficiency as well as the marked stenosis. The left ventricle was somewhat dilated. Its wall measured 1.5 cm in thickness. The endocardium was smooth, lustrous, and transparent. The aortic valve was normal. The coronary arteries and aorta were completely normal.

Abdominal Cavity: The liver was of normal size, but the anterior and superior surfaces of the right lobe were tightly adherent to the diaphragm by fibrous

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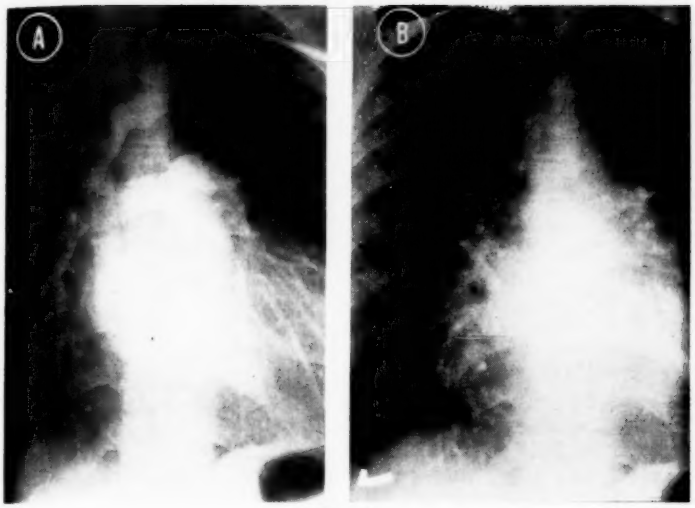

Fig. 5

Fig. 6

FIG. 5. Angiocardiograms demonstrating (*A*) the almost normal position and size of the cavities of the right heart; (*B*) early visualization of the left heart. Note the marked thickness of the area between the borders of the cavities and the cardiac silhouette.

FIG. 6. Angiocardiogram showing an enlarged left atrium and an almost normal left ventricle. Again, note the marked thickness of the area between the borders of the cavities and the cardiac silhouette.

adhesions. Section disclosed a uniform yellow color throughout. The lobules were well preserved.

MICROSCOPIC FINDINGS

The pericardium was tremendously thickened by dense collagen fibers, but there was no evident inflammatory process or tuberculosis. The mitral valve revealed marked thickening of the cusps, particularly near the point of attachment to the ring. Another section showed replacement of the valve ring by dense collagen in which there were calcific deposits. The left ventricle showed an acute inflammatory area about the suture line and some epicardial thickening due to collagen tissues. No Aschoff nodules or evidence of myocarditis was observed.

In the liver there was moderate central vein congestion and a mild fatty infiltration in the parenchymal cells of the central zone. The portal fields showed no change.

ANATOMIC DIAGNOSIS

(1) Status postthoracotomy for repair of myocardial laceration; (2) chronic inactive rheumatic mitral valvulitis with severe mitral stenosis and minimal mitral insufficiency; (3) pericardial fibrosis; (4) fatty infiltration of the liver.

Reports of Chronic Pericardial Effusion with Various Associated Conditions

Pericardial effusions of the chronic variety are uncommon occurrences. An attempt will here be made to categorize some of the previously reported cases on the basis of their most prominent clinical and/or pathologic findings. The cases which will be reviewed are by no means the first or only one of any variety, but are representative examples of the type under discussion.

MYXEDEMA

Freeman's case was that of a 39-year-old male with a low basal metabolic rate, a large heart, and clinical evidences of hypothyroidism.[8] The patient was known to have a pericardial effusion for at least four years, proved by repeated pericardiocentesis. Treatment with thyroid extract resulted in a decrease of the cardiac size to normal in about two months.

Feasby's patient was very similar. A female known to be myxedematous had hypometabolic symptoms for three years and cardiac symptoms for two years with an enlarged heart.[9] Fluid was aspirated from the pericardium. Treatment with thyroid extract resulted in a decrease of the heart size to normal and general clinical improvement.

Silverstone reported on a patient who was made hypothyroid after surgery for Graves' disease.[10] This patient had an idiosyncrasy to thyroid medication so that good metabolic control was impossible. This patient had an effusion for many years with intermittent attacks of acute tamponade.

Comment: The above are well-documented cases of hypothyroidism associated with chronic pericardial effusions. Unfortunately there were no statements in the protocols concerning the character of the pericardial fluids.

CHOLESTEROSIS OF THE PERICARDIUM

Howard's case was that of a 57-year-old female who had clinical ascites and heart failure of one year's duration, and died soon after admission to the hospital.[11] The postmortem revealed Riedel's struma involving the entire thyroid gland and a 4,000 ml pericardial effusion containing yellow cholesterol crystals. The epicardium and pericardium were covered with soft, yellow conelike deposits of cholesterol.

Ada reported the case of a 27-year-old female with a BMR of plus 7, a cholesterol of 107 mg/100 ml, and no evidence of hypothyroidism, but with a large cardiac silhouette.[12] Pericardiocentesis of 2,200 ml of an opalescent fluid produced little change in the heart size. Four years later, without change in the cardiac size, a pericardiectomy was performed. The surgical specimen revealed many areas replaced by masses of cholesterin and large numbers of foreign-body giant cells.

Yu reported a case with proved diagnosis of pericardial effusion of two years' duration in which, upon operation, deposits of cholesterol and a foreign-body reaction were observed in the resected pericardium.[13]

Moe reported a case in which, in 1949, a large heart was discovered and proved by puncture to be caused by an effusion.[14] Five years later, at postmortem, the heart itself was only slightly enlarged, but the pericardial cavity contained 2,500 ml of fluid of the cholesterol variety.

Comment: This group of cases is characterized by the finding of cholesterol deposits in the pericardium. The first example may have been associated with hypothyroidism, but no etiologic factors were determinable in the last three cases.

THORACIC TRAUMA

Barker discussed a patient who was kicked in the chest by a horse in 1943.[15] A year later he was found to have right-sided congestive heart failure. In 1946 a diagnostic pericardial tap was performed. The patient died in 1948 with some enlargement of all chambers of the heart plus a large pericardial effusion.

Ada reported the case of a male who was kicked in the chest three months before symptoms of congestive heart failure developed.[16] A bloody pericardial effusion was discovered, and three months later a pericardiectomy was performed in an attempt to prevent further symptoms.

Dijou reported the case of a 19-year-old soldier who sustained trauma to the chest.[17] One month later an enlarged cardiac silhouette was discovered. Two months later the patient developed signs of congestive heart failure. The patient was operated upon and a large hemorrhagic pericardial effusion was evacuated. A small scar at the apex of the left ventricle was observed. The pericardiectomy resulted in cure.

Comment: Pericardial effusions following trauma to the chest wall are very commonly hemorrhagic. The source of the bleeding may possibly be from the pericardium or the myocardium. Symptoms of tamponade usually develop early (four to six weeks). Many surgeons feel that pericardiectomy should be undertaken at an early time because of the tendency for the formation of an adhesive pericardium after spontaneous resolution of the effusion.

TUBERCULOSIS

Stepman's case was that of a bacteriologically proved example of tuberculous pericarditis in which pericardial aspirations were performed over a period of 16 months.[18] Peel's case 5 had a proved tuberculous pericardial effusion of about eight months' duration.[19] Ellman's case 2 (not bacteriologically proved) was reported to have improved over a period of three years.[20]

Comment: Although tuberculosis is always one of the primary considerations in any undiagnosed pericardial effusion, analysis of many reviews of this subject fails to reveal many patients who had a pericardial effusion for longer than a few months[21,22] (the aforementioned cases being exceptional). It is known that effusion is only one phase in the course of tuberculous pericarditis. Healing, whether spontaneous or with chemotherapy, is a fibrotic and/or adhesive process.

ARTERIAL HYPERTENSION

In his text Wood states that pericardial effusions of unknown cause may remain virtually unchanged for years.[23] He comments on six of his personal patients with this syndrome, all of

whom had essential hypertension, and in two the hypertension was malignant.

COLLAGEN DISEASES

The presence of effusions in lupus erythematosus, scleroderma, scleredema, and periarteritis nodosa has been described.[24] It is the impression of others and myself that these effusions herald activity of the underlying disease or are part of the terminal event in the illness.[25,26]

CARDIAC AND PERICARDIAL NEOPLASMS

Involvement of the heart and pericardium with metastatic malignancy is not infrequent. The production of a pericardial effusion secondary to this involvement results invariably in an acute tamponade.[25] Exceptionally a patient may carry an effusion for several years, as in Blemenfeld's patient, who was treated with x-radiation for metastases to the pericardium from a primary carcinoma of the breast.[27]

Primary tumors, malignant or benign, of the heart and pericardium are extremely infrequent. Although cardiomegaly may be one of the initial findings, the enlargement is rarely on the basis of a diffuse pericardial effusion.

Chronic Pericardial Effusion of Unknown Etiology and with No Specific Pathologic Changes

Cantro's case was that of a 7-year-old child who was known to have had a large heart for three years.[28] Angiocardiography demonstrated the presence of small intracardiac chambers. Antituberculosis therapy resulted in no change of the cardiac size.

Soloff discussed a 46-year-old patient who had progressive cardiac enlargement over a period of eight years.[29] Pericardiocentesis of 1 L of serosanguineous fluid produced no change. Treatment with corticoids was successful. This patient has refused surgical exploration.

Mannix reported on five patients with pericardial effusions which had been present from three months to two years before surgery.[30] Only nonspecific changes were observed in the surgical specimens.

Goldner discussed the history of a 44-year-old Negro male who had symptoms of congestive heart failure for one year and who was known to have an increased cardiac size at the onset of symptoms.[31] Pericardiocentesis of 1 L of fluid produced no marked change. The patient was operated upon and no etiology for the effusion could be determined. One year after surgery the patient was reported to be doing well.

Comment: This group is the inevitable catch-all, since the cases have no resemblance to those in the previous categories or to each other.

Discussion

The only reference to the presence of a chronic pericardial effusion associated with rheumatic heart disease is one not discussed in the above review. In this case Voldet, at postmortem, observed a hemorrhagic effusion with microscopic cholesterol crystals in a patient with chronic congestive heart failure and tight mitral stenosis.[32] However, in the 15 years that this patient was treated, she refused all diagnostic tests, so that the pericardial effusion, which was of questionable chronicity, may have been a terminal event.

In neither Voldet's case nor the present one is there any basis for making a direct association between the pericardial effusion and rheumatic activity. It has been amply shown that in acute rheumatic pericarditis the process is a fibrinous one and, if resolution is not complete, results in milk spots, adhesions, or calcification.[33,34] While chronic congestive heart failure was definitely present in Voldet's patient, there is ample clinical and hemodynamic evidence to deny this in the present case. Other pathologic associations, such as with hypothyroidism, trauma, tuberculosis, neoplasm, hypertension, or collagen disease, could not be made. In the final analysis one can only add the present report to the general group of those with no specific etiologic or pathologic findings.

Summary

A patient with a chronic pericardial effusion of at least three years' duration is presented, in whom there was associated chronic mitral valvular disease.

No clinical, laboratory, hemodynamic, or pathologic evidence was found to demonstrate any direct association between the pericardial effusion and the underlying rheumatic heart disease.

The syndrome of chronic pericardial effusion is reviewed and a simple classification proposed.

Acknowledgments

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Pericardiocentesis with the Aid of a Plastic Catheter and ECG Monitor*

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IN PERICARDIOCENTESIS the needle may cause injury of a coronary vessel, laceration of the myocardium, ventricular tachycardia or fibrillation, gastric puncture, pneumothorax, and shock. Furthermore, the tap may be nonproductive in the presence of an effusion; or an extracardiac effusion may be drained under the impression that it originates in the pericardial sac. Any improvement of the technique to minimize these complications would be welcome.

This report describes how the routine use of a plastic catheter may be useful in performing a pericardial tap. It permits a careful and studied aspiration and air insufflation, because the soft catheter may be safely left in the sac for an extended period. Hitherto, the knowledge that a sharp needle within the sac was near the myocardium would force the operator to rush the procedure. The drainage would tend to be incomplete and the air insufflation could not be checked by x-ray examination before removing the needle. The plastic catheter was suggested by a report of Kaslow and associates,[1] who described its use in pleural taps.

This report also describes our experience with the ECG monitor according to the method of Bishop, Estes, and McIntosh.[2] They used the needle as an exploring electrode. Contact of the needle with the myocardium was indicated by elevation of the ST segment. This, they stated, was an indication for withdrawing the needle, since it indicated there was no cushioning layer of fluid between the pericardium and myocardium. We have arrived at a somewhat different concept of the usefulness of the ECG monitor.

TECHNIQUE

The tap is done with the patient sitting, if possible. This long-favored posture has recently received additional support from angiocardiographic studies[3] which showed that the fluid tends to lie anteriorly and the heart posteriorly in this posture. The point of entry was precordial in all patients except one where Marfan's subxiphoid approach was used. However, any point of entry and any posture permits the use of the catheter and electrocardiogram.

The following needle and polyethylene catheter combinations may be used: #14 thin-wall needle with PE 190 tubing; #16 thin-wall needle with PE 90 tubing; and #18 thin-wall needle with PE 50 tubing. The tubing comes already sterilized in 12- and 36-inch lengths. The longer length is preferable because it permits more of the tube to be introduced into the pericardium. The distal 3 cm of the tube may be fenestrated for better drainage. It can be done by bending the tube sharply and snipping off a tiny corner.[4] One should take care not to cut too big a hole, or the tubing may be so weakened that it will break off within the chest.

The choice of needle is determined by the amount and type of fluid which is expected. The large-bore needle permits the introduction of a large-bore catheter which facilitates aspiration. Aspiration through the narrower tubing can be very tedious if the fluid is not very thin. On the other hand, the large needle produces more trauma. If a large effusion is definitely present, the larger needle should be used; for exploratory taps, start with the thinner needle.

The needle should be rotated like a drill during its insertion. This reduces the pressure needed to push the needle through the skin and tissues, thus lessening the pain considerably. The needle is connected to the recorder by means of a sterilized wire with clips on each end. It serves as an exploring electrode. The needle

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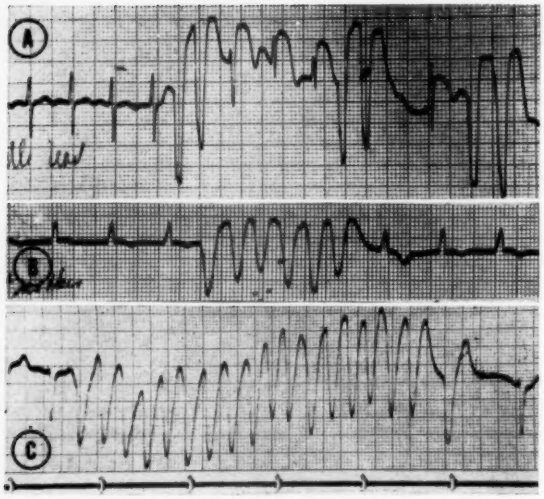

FIG. 1. Needle lead. Signs of contact of needle with heart. QS extrasystoles. (A) The ST segments of the extrasystoles show injury elevation. (C) The longest series of QS extrasystoles encountered (ventricular tachycardia).

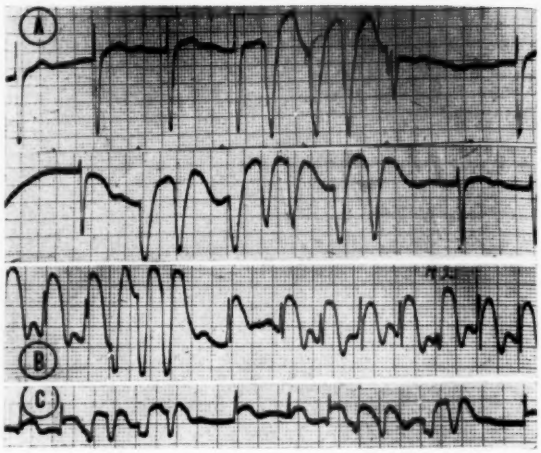

FIG. 2. Needle lead. (A) QS extrasystoles. (B) QS extrasystoles and ST injury elevation in extrasystoles and dominant beats. (C) Note similarity of the two runs of extrasystoles. This could possibly be caused by a repetitive response to a single stimulus.

employed for the infiltration of the local anesthetic should be similarly used because it occasionally penetrates deeply enough to touch the heart.

The electrocardiograph must be a direct-writer. A two-channel machine is advantageous because sometimes the needle lead is distorted by artefacts. Then, the second channel, recording a limb or precordial lead, can still manifest the changes clearly. This applies especially to extrasystoles and other arrhythmias.

The monitor looks for evidence of the needle's touching the heart. In the needle lead this consists of elevation of the ST segment and ventricular extrasystoles with a QS form (Figs. 1 and 2). If the needle should impinge on the auricular myocardium there is an elevation of the T_a segment and auricular extrasystoles with a negative P wave. The limb leads do not show the ST deviations; the extrasystoles are of course readily seen in the limb leads but have no characteristic form there, so that it is not possible to know whether they are needle-induced or spontaneous.

The deflections in the needle lead are so large that they necessitate a reduction of the amplification to about 0.3 normal standardization. The ST deviations are often striking and easily recognized. At other times the movement of the needle causes such violent fluctuation of the base line that the recorder cuts out. The procedure must be stopped at that point until the tracing becomes legible. The ST changes may be less pronounced and difficult to diagnose promptly, especially when the base line is not stable.

When the monitor detects an ST elevation or contact extrasystoles he reports them. However, as will be explained, they do not constitute absolute indications for withdrawing the needle. The operator should continue to advance the needle deeper until he obtains either blood or fluid. Blood in conjunction with an ST elevation or QS extrasystoles indicates penetration into a ventricle. There is a tendency to advance the needle faster than the tracing can read. This must be corrected by advancing the needle millimeter by millimeter upon command of the monitor.

During the insertion of the needle and also during its withdrawal, suction is frequently applied with a 10-ml syringe attached to it. When fluid is obtained that is not frank blood, the syringe is removed and the plastic catheter is passed through the needle. If the tip of the needle lies in a cavity, the catheter will pass easily; otherwise it will meet with resistance. Fifteen or more centimeters of the tubing should be placed within the chest. The needle is now withdrawn over the catheter so that the latter now lies alone in the chest and presumably in the pericardial sac. Since there is no longer any danger of traumatizing the heart, a leisurely and careful aspiration and insufflation can be done. Air should be injected following the

aspiration in order to verify the site of the effusion. In two instances we were surprised to find that the needle had tapped extracardiac effusions.

The catheter should never be pulled out of the needle because its distal end may be sheared off by the needle's cutting edge.

Results

Fifteen patients were tapped. Of these 15, 9 yielded fluid; in 8 of these a plastic catheter was inserted; and in 7 of the 9, air was injected; of the 7, roentgen examination showed the air to be in the pericardial sac in 5, and in 2 the fluid proved to be extracardiac and the air was found in the pleural cavity.

Of 3 cases in which fairly large amounts of fluid (750, 400, and 250 ml) were found and in which the pericardial origin of the fluid was proved by the subsequent pneumopericardium, only one showed no evidence of contact between the needle and the myocardium; one showed ST elevation and QS extrasystoles and one showed only ST changes. Of the 4 cases yielding smaller amounts of pericardial fluid, all showed ST elevations and 3 showed QS extrasystoles. Five of the 6 cases in which no fluid was obtained showed both ST elevations and QS extrasystoles. One showed only ST changes. The two cases of extracardiac drainage showed neither ST elevations nor QS extrasystoles. No auricular changes were seen.

One patient suffered a sinoauricular standstill during the infiltration of the pleura with procaine. This is described in detail in the Discussion.

Discussion

Advantages of Plastic Catheter: The plastic catheter permits a safe, unhurried aspiration and insufflation. One can introduce antibiotics, radioactive solutions, and other medications through the tube. There was no evidence that the tubing ever caused any significant trauma to the myocardium; nor would it be expected to do so, since it has such a soft consistency. In one patient, during the aspiration of fluid through the catheter a run of five ventricular extrasystoles appeared in the limb lead monitoring the aspiration. It is doubtful that the soft tubing could have been sufficiently irritating to induce them.

Sometimes fluid is obtained not during the insertion of the needle but only during its withdrawal. We have observed a behavior of the pericardium in the cadaver which explains this. The advancing needle indents the parietal pericardium and presses it against the visceral layer. It tends to push away any fluid which might lie between the walls of the pericardial sac. However, when the needle is being withdrawn, the parietal layer tents away from the visceral and fluid flows into the tent. This behavior of the pericardium also explains some of our electrocardiographic findings.

Significance of ST Changes: In the original report of Bishop and associates[2] it was shown that the pressure of the needle on the myocardium through an intact pericardium causes the same ST elevation as when the needle lies in the myocardium itself. It was stated that the fluid would cushion the parietal pericardium and prevent the needle from pressing on the myocardium, thereby preventing the appearance of ST changes. According to this reasoning an ST elevation in the needle lead was an indication to withdraw the needle. It meant the needle had penetrated the parietal pericardium and, since no fluid was obtained, that there was no fluid present. Or, it meant that the needle was pressing on the myocardium through an intact pericardium which was not cushioned by fluid.

In our limited experience we have obtained 250 ml of fluid in one patient *after* the appearance of an ST elevation and QS extrasystoles. In 4 other patients we obtained smaller amounts after similar changes. We would have been in error had we assumed the absence of fluid when such injury signs appeared in the tracing. In only one patient, who yielded 400 ml of fluid, did the tracing fail to manifest evidence of myocardial irritation.

The cushioning effect of fluid is probably not very effective unless the fluid is under great pressure, is present in large amounts, or the parietal pericardium is very thin. In our experience most taps which have yielded pericardial fluid have irritated the myocardium. Therefore, the absence of both ST elevation and QS extrasystoles during the procedure should arouse the suspicion that the pericardium has not been touched by the needle. It is clear that even with the aid of the needle lead the operator cannot define precisely the position of the needle point with respect to the pericardium and epicardium.

Ventricular Arrhythmias: Bishop and associates[2]

did not mention the induction of extrasystoles by the needle. We noted them in 8 cases (see Figs. 1 and 2). The needle lead showed large QS complexes, as would be expected if the needle were both the stimulating and recording electrode. Occasionally RS complexes appeared. Their origin is not known; some may have been induced by the QS extrasystoles.[5] Often the extrasystoles appeared in runs. The longest series lasted 4 seconds and could be classified as a ventricular tachycardia (Fig. 1*C*). Sometimes they did not have clearly defined QRS and ST-T complexes and were multiform. The resemblance to ventricular fibrillation is frighteningly obvious. It is indeed surprising that fatal ventricular fibrillation does not occur more often when the myocardium is punctured. Greene and associates[6] have reported ventricular extrasystoles during the percutaneous puncture of the ventricles. Groedel and Borchardt[7] recorded similar extrasystoles by irritating the outside of the parietal pericardium during thoracoscopy.

Other Arrhythmias: In one patient the infiltration of the pleura with procaine caused a sinoauricular standstill. After an undetermined but short interval the A-V node became the pacemaker with a rate of 40 per minute. At this point the disturbance was noted in the tracing and the needle was ordered removed. A few seconds later the patient became apprehensive, faint, and sweaty. Normal rhythm reappeared in about 20 seconds and the symptoms disappeared. The procedure was resumed and completed without further incident.

As this case illustrates, the early detection of an arrhythmia leads to early treatment before the arrhythmia lasts long enough to cause damage. Many cases of "sudden" death during operative procedures are preceded by an undiagnosed prolonged period of anoxia or inefficient heart action. Prompt diagnosis leads to early treatment and prevention of such accidents. The early diagnosis of arrhythmias is the most important function of ECG monitor.

Motion of the needle imparted by the heart's motion is a well-known sign of direct contact of the heart with the needle. We have encountered an instance of movement of the needle not accompanied by ST changes or extrasystoles. Could this motion have been transmitted to the needle through extracardiac tissue? We mention this because it is important to know when the needle is touching the pericardium, when it has penetrated the pericardium, and when it is lying in the myocardium. Neither the classic sign of needle motion nor the new electrocardiographic signs can make such distinctions. Since one cannot know when the needle is touching the bare myocardium, one cannot avoid injuring the latter in many cases. Usually this is of no clinical consequence, but unfortunate exceptions are bound to occur.

Summary

A plastic catheter is useful in pericardiocentesis. After the needle has entered the sac as evidenced by the aspiration of fluid, the catheter is passed through the needle. The latter is removed, leaving the catheter in. Aspiration and insufflation can now be done in a careful and studied manner because the indwelling soft tubing cannot injure the myocardium.

Observations on the cadaver have shown that the advancing needle indents the parietal pericardium before piercing it. On pulling out, the needle tents it. The tenting explains why fluid may be obtained only during the withdrawal of the needle.

The ECG monitor should be part of every tap, because it detects arrhythmias early and leads to their prompt correction. It will thereby prevent the type of sudden death which occurs subsequent to a period of ventricular tachycardia and fibrillation or to a period of asystole. For this any lead suffices. A special lead using the needle as the exploring electrode is preferred because in addition to detecting arrhythmias it also indicates the proximity of the needle to the heart.

When the needle impinges on the myocardium, the needle lead shows an elevated ST segment and QS extrasystoles. The latter are characteristic of extrasystoles induced by the needle when it acts both as an irritant and as an electrode. They have not been previously described in this context. The appearance of these signs of contact when fluid is being aspirated indicates that the fluid is pericardial in origin. Thus, the needle lead helps to identify the source of an aspirate.

The signs of contact may appear when the needle has not penetrated but only indented the parietal pericardium into the myocardium. Evidence is presented here that even when an effusion is present these signs may appear before the pericardium has been penetrated. Accordingly, if one wishes to avoid a dry tap, it is

necessary to advance the needle in spite of the signs of contact. This must lead to needle injury of the myocardium which, fortunately, is usually insignificant. But where the myocardium is thinned or soft it can cause a serious laceration. One should be aware that the needle lead does not reduce the risk in this respect.

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Clinical Study

Effects of Lanatoside C on Cardiovascular Hemodynamics

Acute Digitalizing Doses in Subjects with Normal Hearts and with Heart Disease Without Failure*

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SINCE the use of foxglove in dropsy by Withering,[1] digitalis glycosides have been used widely in the treatment of heart failure and their effects have been subject to extensive clinical, experimental, and physiologic investigation.

Numerous studies utilizing the technique of right heart catheterization have established some of the effects of cardiac glycosides on cardiovascular hemodynamics in patients with heart failure.[2–8] However, a survey of the literature reveals only few studies[5–7,9–12] with limited numbers of patients with normal hearts or patients with heart disease without heart failure. In these studies it was found that cardiac glycosides in normal individuals either decreased the cardiac output[7,9,10,12] or caused no significant change.[5,6] Similar results were obtained in patients with enlarged hearts without evidence of heart failure[5,6,10,11] except for one case[10] in which cardiac output was increased. Most of the previous studies do not include criteria by which changes in cardiac output can be attributed to the drug as opposed to random variations.

The present study was undertaken to reevaluate the effect of digitalis glycosides in subjects with normal hearts and in patients with heart disease without evidence of heart failure. Patients with heart disease but not in failure are frequently considered for prophylactic digitalization prior to major surgery or other types of unusual stress. If no deleterious effects on the cardiovascular hemodynamics are demonstrated, such therapy might well be justified.

This report presents the early effects of lanatoside C on the cardiovascular hemodynamics in 11 patients studied by the technique of right heart catheterization. To establish criteria for the determination of significant changes in cardiac output that could be attributed to the drug, 100 right heart catheterizations in which two cardiac output determinations were done within 9 to 91 minutes (average 36 minutes) without any drug administration were analyzed.[13] On the basis of this study the ranges of allowable spontaneous variations under "steady state" conditions were determined.

MATERIALS AND METHODS

Seven subjects without heart disease and four with heart disease but not in heart failure were studied (Tables I and II). Four of the seven subjects without heart disease were males and three were females.

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Their ages ranged from 25 to 58 years. In the other group there were two males and two females, their ages ranging from 49 to 63 years. All had normal sinus rhythm. The electrocardiograms were within normal limits except one (case 11) which had some nonspecific T wave changes. In the group with heart disease cardiac enlargement was absent or slight on x-ray examination.

The patients were studied in the resting state after fasting for at least twelve hours. They were hospitalized at least three days before the study was done. They all received phenobarbital 0.06 Gm and Nembutal 0.1 Gm the evening before any observations were made. None had received cardiac glycosides in the past.

The physiologic data were obtained by utilizing the technique of right heart catheterization. The blood oxygen content and capacity were determined by the method of Van Slyke and Neill.[14] The expired air was collected in a Tissot spirometer and analyzed in the Scholander gas analyzer.[15] The cardiac outputs were determined by the direct Fick principle. Pressures were recorded using Sanborn electromanometers and a direct-writing Sanborn Poly-Viso recorder. Mean pressures were determined by planimetric measurement of the electrically integrated pressure tracings using one or more complete respiratory cycles. The point of zero reference for measurement of central pressures was 5 cm below the angle of Louis with the patient in the supine position. Total pulmonary artery and total peripheral arterial resistances were calculated according to the following formula:[16,17]

$$\frac{\textit{Mean pressure mm Hg} \times 1.332}{\textit{Cardiac output cc/sec}} = \textit{Resistance in dynes sec cm}^{-5}.$$

Control measurements were made after the catheter and the venous and indwelling arterial needles were inserted and the patient was quiet for at least fifteen minutes. Two control cardiac outputs were taken in three patients and one control cardiac output in the others (Tables III and IV). Lanatoside C, 1.2 to 1.6 mg (as noted in Tables III and IV), was injected slowly through the catheter into the pulmonary artery over a two-minute period. Cardiac outputs were then obtained from 40 to 121 minutes later. Multiple pressure measurements were recorded throughout the study.

QT_c intervals were measured in six cases before and after lanatoside C injection (Table V).

The criteria for interpretation of the results are based on a study in our laboratory of the "steady state," using the direct Fick principle.[13] According to this analysis, any change in cardiac output within the range of plus or minus 15 per cent should not rightfully be attributed to drug effect. Changes within this range can be due to the inherent experimental error of the technique.

Results

Heart Rate: In the two groups of patients, there was no significant change in the heart rate. In 4 out of 11 cases a decrease up to 4 beats per minute was noted. The remainder of the patients showed an increase up to 9 beats per minute. QT_c intervals in the six cases measured showed a decrease, indicating digitalis effect electrocardiographically (see Table V).

Oxygen Consumption: Control oxygen consumptions (see Tables III and IV) were normal as compared to the generally accepted figure of 138 ± 14 cc/min/sq. M BSA except for cases 1 and 4 whose values were slightly but not significantly above normal. Oxygen consumption calculated at different time intervals following digitalis administration did not show any significant changes from control levels. The greatest change was 16 cc.

Cardiac Output: The 7 patients with normal hearts had changes in cardiac indices from control level following digitalization ranging from +13 to −13 per cent (see Table I and Fig. 1). In the second group, the patients with heart disease without evidence of heart failure, the change from control levels ranged from −11 to +13 per cent (see Table II and Fig. 1). On the basis of analyses of previous experiences in our department,[13] differences of the order cited above are within the limits of expected variation (Fig. 1).*

Two patients without heart disease and one patient with heart disease without heart failure (cases 6, 7, and 10) had two control cardiac output determinations (Fig. 2).* These cases demonstrate the value of at least two control cardiac output determinations in this type of study. Control cardiac indices and cardiac indices at different time intervals following digitalization are shown in Tables III and IV. If the control cardiac indices of higher value are considered, two (cases 6 and 10) show significant fall and one (case 7) shows insignificant fall after digitalization (see Fig. 2). However, when cardiac indices with lower values are considered, this impression is not corroborated. In case 6, 97 minutes after digitalization there was a fall in cardiac index of 19 per cent from the second control level. If the first control cardiac index is taken, then there is only a negligible change of 3.5 per cent. In case 10, the fall in cardiac indices from initial control level (cardiac index with higher value) was also significant (−24 per cent) following digitalization. However, if

*See page 95.

TABLE I

Measurements of the Circulation in Seven Patients Without Heart Disease During Acute Digitalization Studies

Case	Clinical data	Time (min)	Brachial or femoral artery pressure (mm Hg)		Pulmonary artery pressure (mm Hg)		Right ventricular pressure (mm Hg), S/D	Right auricular pressure (mm Hg), M	Peripheral venous pressure (mm Hg), M	Cardiac output (L/min)	Stroke volume (cc)	Heart rate (beats/min)
			S/D	M	S/D	M						
1	F. D.; M, age 58; G-I disease undiagnosed; no heart disease	Control	141/75[c]	102	25/8	14	—	—	—	—	—	—
			138/75	104	25/8	15	24/—	3	—	7.07	110.5	64
		55[a]	155/75	108	25/8	15	—	—	—	7.31	114.0	60
2	M. F.; F, age 44; multiple sclerosis, argyria; no heart disease	Control	110/61[c]	80	21/8	—	21/4	4	—	4.91	71.2	69
			110/64	82	—	8	20/3	—	—	—	—	—
		30[b]	113/62	80	18/3	7	—	2	—	—	—	—
		58	124/70	89	20/5	9	19/1	2	—	4.48	65.8	68
		88	128/72	—	—	—	24/2	—	—	—	—	—
		103	127/77	97	—	—	—/3	2	—	4.60	63.8	72
3	M. M.; F, age 57; carcinoma of the breast with metastases; no heart disease	Control	132/62[d]	83	32/10	15	32/5	1	4.9	5.13	75.3	68
			—	—	—	—	31/5	—	—	—	—	—
		20[a]	145/67	94	26/9	10	26/1	2	5.6	—	—	—
		29	154/72	—	—	—	32/—	—	—	—	—	—
		43	142/69	95	—	—	21/1	—	4.4	5.71	77.2	74
		80	153/65	91	—	—	26/—	—	4.4	—	—	—
		95	137/62	87	—	—	22/1	1	4.4	4.44	67.3	66
4	J. M.; M, age 37; no heart disease	Control	137/70[d]	93	20/5	13	21/3.5	—	8.6	—	—	—
			139/75	99	23/7	14	25/4.0	—	7.9	8.92	131.0	68
			118/61	79	22/6	16	—	—	7.8	—	—	68
			—	—	—	14	—	—	6.9	—	—	—
		17[a]	116/57	72	—	14	—	—	6.9	—	—	—
		73	—	—	—	14	—	—	7.6	—	—	—
		80	121/68	83	—	14	—	—	6.6	8.64	123.5	70
5	J. C.; M, age 28; diabetes mellitus; no heart disease	Control	100/55[d]	70	18/8	11	17/2	—	4.7	5.27	88.0	60
			107/68	78	18/8	12	20/2.5	—	4.8	—	—	—
		14[b]	104/63	75	—	—	18/2	—	4.4	—	—	—
		26	103/63	74	—	—	20/2	—	5.0	—	—	—
		37	97/61	73	—	—	18/3	—	5.0	—	—	—
		54	103/50	67	—	—	18/4	—	4.3	—	—	105
		90	96/60	72	—	—	16/2	2.7	4.6	5.98	61.7	97

Table I (*Continued*)

6	M. M.; F, age 53; no heart disease	Control	158/78[d]	108	26/15	18	28/7	4.8	7.0	6.0	73.0	82
			158/74	105	27/15	18	30/8	—	7.0	6.96	83.0	84
		20[a]	—	—	27/11	16	28/6.5	—	7.4	—	—	—
		49	153/70	100	27/13	17	30/5	—	7.2	6.37	79.6	80
		73	159/72	103	27/13	—	27/4	—	7.6	—	—	—
		92	157/72	97	27/13	—	27/3	—	6.8	—	—	—
		97	152/69	97	24/11	15	—	3.3	—	5.78	71.5	81
7	B. R.; M, age 25; no heart disease	Control	135/74[d]	96	—	—	30/4	3.9	6.2	8.10	86.0	94
			162/92	113	—	—	32/4	3.0	6.5	—	—	—
			148/76	98	—	—	30/4	3.2	6.6	7.25	78.0	93
		21[a]	159/83	108	—	—	32/5	2.9	6.0	—	—	—
		30	138/71	97	—	—	—	2.2	6.9	—	—	—
		54	—	—	—	—	31/2	1.2	6.3	—	—	—
		83	146/87	106	—	—	29/3	1.2	—	—	—	—
		92	149/78	102	—	—	32/3	—	7.0	7.53	74.5	101
		116	—	—	—	—	31/2	1.5	7.5	—	—	—
		123	148/82	104	—	—	30/2.5	1.2	6.2	7.50	73.7	103

S/D = systolic/diastolic. M = mean.
[a] Minutes after 1.6 mg lanatoside C. [b] Minutes after 1.2 mg lanatoside C. [c] Brachial artery. [d] Femoral artery.

the other control cardiac index is considered in comparison with those determined after digitalization, the change was then only −4 per cent. Case 7 also demonstrates the same kind of variations but to a lesser degree.

Apparent changes in cardiac indices in cases 6 and 10 arise from significant differences in the two control cardiac indices. Figure 2 shows that there never was a continuous trend in any direction. These figures fall outside the range of "normal variations" previously determined in patients in the "steady state."[13] This indicates that during determination of at least one of these control cardiac outputs, the patient's state was changing in spite of the absence of any significant change in oxygen consumption or heart rate. Therefore, if two control cardiac output determinations were not obtained, a change in cardiac output due to a change in state might falsely have been attributed to the effect of digitalis.

Right Heart and Pulmonary Artery Pressures: Right ventricular end-diastolic and mean right auricular pressures were within the accepted normal values, except in case 6. In cases 3 and 6 end-diastolic pressures in the right ventricle fell 4 mm Hg in each without significant change in cardiac output. Right auricular pressures, in 5 of the 6 patients in whom multiple mean measurements were obtained (cases 2, 6, 7, 8, and 11), fell 1 to 3 mm Hg, and in the other there was no change.

Peripheral venous pressures were measured in 7 cases and did not show any change following lanatoside C. Three of these showed a slight fall in right auricular pressure.

There were no significant changes in right ventricular systolic and/or pulmonary artery pressures after drug administration except in case 3, where there was a slight fall in right ventricular systolic pressure.

Systemic and Pulmonary Arterial Pressure and Resistance: Systemic and pulmonary arterial pressure and resistance varied slightly but in no consistent fashion. These variations were well within the expected range.[4]

Arteriovenous Oxygen Difference: No significant change was observed in the arteriovenous oxygen differences after digitalization in any patient, although in 10 of the 11 cases there was a tendency for a minimal increase.

Arterial Oxygen Saturation: Arterial oxygen saturation remained fairly constant following digitalis administration. This condition in-

TABLE II

Measurements of the Circulation in Four Patients with Heart Disease but Not in Heart Failure During Acute Digitalization Studies

Case	Clinical data	Time (min)	Brachial or femoral artery pressure (mm Hg) S/D	Brachial or femoral artery pressure (mm Hg) M	Pulmonary artery pressure (mm Hg) S/D	Pulmonary artery pressure (mm Hg) M	Right ventricular pressure (mm Hg), S/D	Right auricular pressure (mm Hg), M	Peripheral venous pressure (mm Hg), M	Cardiac output (L/min)	Stroke volume (cc)	Heart rate (beats/min)
8	E. S.; M, age 63;	Control	167/88[c]	116	31/9	17	—	4	—	6.0	91.0	66
	? polycythemia;	53[a]	167/80	112	33/8	19	—	1	—	5.32	84.5	63
	ASHD, NSR											
9	J. R.; M, age 49;	Control	—	—	—	35	—	—	8.8	—	—	—
	RHD, NSR, MS &		125/70[d]	92	—	—	45/2	—	7.7	—	—	108
	MI; recurrent hem-		130/77	97	44/25	32	44/2	—	5.2	6.46	68.8	94
	optyses; no CHF	13[a]	127/68	87	43/23	31	43/1.5	—	4.8	—	—	—
		25	—	—	46/23	31	47/2	—	4.8	—	—	—
		40	134/73	93	43/22	31	45/1.5	—	4.9	6.71	70.7	95
		48	130/72	92	—	—	—	—	3.8	—	—	—
		64	125/72	88	43/23	—	43/1	—	3.5	—	—	—
		72	—	—	41/—	29	44/0	—	3.7	—	—	—
		85	126/68	88	—	29	43/2	—	3.2	6.90	70.5	98
		94	143/78	100	42/22	31	45/0	—	3.2	—	—	—
		108	119/58	82	47/27	36	44/2	—	3.2	—	—	—
		121	128/72	92	43/22	30	44/1	2	3.7	6.92	70.7	98
10	H. S.; F, age 56;	Control	—	—	20/—	11	20/4.5	—	—	—	—	82
	ASHD, NSR,		137/65[d]	92	22/9	12	21/3.5	—	—	6.33	77.2	82
	myocardial dam-		132/64	91	22/7	12	18/2.5	—	—	5.04	71.9	77
	age, no CHF	18[b]	136/67	93	—	11	20/4	—	—	—	—	—
		47	132/64	86	19/—	11	18/1.5	—	—	—	—	—
		52	132/67	92	—	11	21/4	—	—	5.39	64.1	84
		58	110/57	76	—	11	20/3	—	—	—	—	—
		97	115/57	78	18/5	11	18/2	1	—	4.82	58.1	83
11	I. K.; F, age 62;	Control	135/66[d]	93	32/12	20	31/2	1.5	5.9	—	—	90
	ASHD, LV hyper-		120/69	85	35/14	23	33/4	—	5.7	6.41	77.3	83
	trophy, myocar-	18[a]	—	—	33/16	23	32/5.5	—	6.2	—	—	—
	dial damage, NSR,	31	155/65	95	36/14	23	33/3	—	5.7	—	—	—
	no CHF; old hyper-	42	—	—	32/12	21	31/3.5	—	4.9	—	—	—
	tension; emphysema;	48	143/60	91	35/13	23	33/0.5	—	6.2	6.30	70.7	89
	bronchial asthma;	82	148/68	96	32/15	22	36/6	—	4.8	—	—	—
	recent broncho-	104	—	—	32/15	25	32/0.5	—	4.7	—	—	—
	pneumonia;	117	150/68	94	—	—	30/2	—	5.7	—	—	—
	diabetes mellitus	120	155/68	95	—	—	32/2.5	0.5	5.7	6.71	70.7	95

[a] Minutes after 1.6 mg lanatoside C. [b] Minutes after 1.2 mg lanatoside C. [c] Brachial artery. [d] Femoral artery.

ASHD = Arteriosclerotic heart disease. CHF = Congestive heart failure. LV = Left ventricle. MI = Mitral insufficiency. MS = Mitral stenosis. NSR = Normal sinus rhythm. RHD = Rheumatic heart disease.

TABLE III

Physiologic Data Concerning Cardiac Output in Seven Patients Without Heart Disease During Acute Digitalization Studies

Case	Body surface area (sq M)	Time (min)	Oxygen consumption (cc/min/sq M BSA)	Respiratory quotient	Cardiac index (L/min/sq M BSA)	A-V oxygen difference (vol %)	Cardiac index (% change)	Arterial blood oxygen			Calculated resistance (dynes sec cm^{-5})	
								Content (vol %)	Capacity (vol %)	Saturation (%)	Peripheral	Total pulmonary artery
1	1.70	Control	179	0.72	4.16	4.3	—	17.6	19.0	92.5	1175	170
		55[a]	189	0.76	4.30	4.4	+ 3.4	17.6	18.9	93.1	1183	164
2	1.36	Control	130	0.75	3.61	3.6	—	15.6	16.0	97.5	1305	—
		58[b]	119	0.79	3.29	3.6	− 8.8	15.6	16.0	97.5	1590	—
		103	135	0.82	3.38	4.0	− 6.4	15.6	16.0	97.5	1685	—
3	1.68	Control	119	0.74	3.05	3.9	—	14.3	15.4	92.7	1295	—
		43[a]	129	0.79	3.40	3.8	+11.5	14.3	15.4	92.7	1330	—
		95	119	0.73	2.65	4.5	−13.1	13.9	—	—	1555	—
4	1.80	Control	178	1.01	4.96	3.6	—	18.6	19.4	95.8	890	126
		80[a]	173	0.81	4.67	3.7	− 5.8	17.9	18.5	96.8	770	130
5	1.45	Control	149	0.82	3.64	4.1	—	15.4	16.2	95.0	1062	—
		90[b]	152	0.83	4.12	3.7	+13.2	14.3	15.2	94.1	963	—
6	1.62	Control	122	0.75	3.70	3.3	—	16.2	17.6	92.0	1440	240
		Control	129	0.72	4.30	3.0	—	15.5	—	—	1205	207
		49[a]	134	0.76	3.93	3.4	+ 6.2[c]	15.4	16.1	95.7	1255	213
		97	129	0.75	3.57	3.6	− 3.5	15.4	16.1	95.7	1343	207
7	1.78	Control	151	0.73	4.56	3.3	—	19.3	19.6	98.3	949	—
		Control	143	0.69	4.07	3.5	—	19.2	19.6	98.0	1080	—
		92[a]	152	0.58	4.23	3.6	+ 3.9[d]	19.0	19.5	97.0	1083	—
		123	143	0.64	4.22	3.4	+ 3.7	18.8	19.5	96.3	1110	—

[a] Minutes after 1.6 mg lanatoside C. [b] Minutes after 1.2 mg lanatoside C. [c] Using first control. [d] Using second control.

TABLE IV

Physiologic Data Concerning Cardiac Output in Four Patients with Heart Disease but Not in Heart Failure During Acute Digitalization Studies

Case	Body surface area (sq M)	Time (min)	Oxygen consumption (cc/min/sq M BSA)	Respiratory quotient	Cardiac index (L/min/sq M BSA)	A-V oxygen difference (vol %)	Cardiac index (% change)	Arterial blood oxygen			Resistance (dynes sec cm^{-5})	
								Content (vol %)	Capacity (vol %)	Saturation (%)	Peripheral	Total pulmonary artery
8	1.58	Control	167	0.70	3.80	4.4	—	19.3	20.2	95.7	1545	227
		52[a]	169	0.73	3.37	5.0	−11.3	19.1	20.2	94.6	1685	286
9	2.11	Control	144	0.80	3.06	4.7	—	14.3	14.8	96.6	1200	396
		40[a]	146	0.85	3.18	4.6	+ 3.9	14.2	14.8	95.9	1110	350
		85	160	0.80	3.27	4.9	+ 6.9	14.5	14.8	98.0	1020	336
		121	157	0.74	3.28	4.8	+ 7.2	14.1	14.8	95.2	1065	347
10	1.62	Control	125	0.70	3.91	3.2	—	14.6	15.0	97.3	1162	152
		Control	127	0.71	3.11	4.1	—	14.6	—	—	1445	190
		52[b]	130	0.73	3.33	3.9	+ 7.1[c]	14.3	—	—	1365	163
		97	131	0.73	2.98	4.4	− 4.2	14.4	14.6	98.6	1295	182
11	1.65	Control	175	0.75	3.89	4.5	—	15.9	18.5	86.0	1060	287
		48[a]	183	0.74	3.82	4.8	− 1.8	15.9	—	—	1155	292
		120	191	0.75	4.07	4.7	+13.3	15.9	18.5	86.0	1123	—

[a] Minutes after 1.6 mg lanatoside C. [b] Minutes after 1.2 mg lanatoside C. [c] Using second control.

cludes the one patient (case 11) who had arterial oxygen unsaturation due to chronic pulmonary disease.

Discussion

Among the cases with heart disease none showed hemodynamic evidence of heart failure. There was only one case (case 9) with a moderate degree of pulmonary hypertension, and two cases (cases 8 and 11) with slight elevation of pulmonary artery pressure. Case 9 had rheumatic heart disease with mitral stenosis and mitral insufficiency; cases 8 and 11 had pulmonary emphysema. Case 11 had some arterial

TABLE V
The Average QT_c Interval Before and After Cedilanid

Case	Time (min)	QT_c Interval (sec)
2	Control	0.412
	66[a]	0.335
	88	0.334
3	Control	0.453
	Control	0.437
	60[b]	0.349
	80	0.418
	105	0.331
4	Control	0.436
	Control	0.440
	23[a]	0.387
	61	0.353
	80	0.332
6	Control	0.417
	Control	0.418
	49[b]	0.405
	97	0.394
7	Control	0.363
	Control	0.344
	38[b]	0.342
11	Control	0.460
	Control	0.420
	17[b]	0.312
	35	0.276

[a] Minutes after 1.2 mg lanatoside C. [b] Minutes after 1.6 mg lanatoside C.

blood oxygen unsaturation. Normal right ventricular end-diastolic pressure, normal control cardiac output without any increase after digitalization, and absence of any significant change in the pulmonary artery pressure following digitalis administration in these patients would be hemodynamically inconsistent with congestive heart failure.

In three (cases 3, 6, and 7) of the group of subjects without heart disease, pulmonary artery or right ventricular systolic pressures were close to abnormal levels. Case 7 was a 25-year-old man who did not have any clinical evidence of lung or heart disease. The control right ventricular systolic pressures ranged between 28 and 32 mm Hg. In case 6, right ventricular end-diastolic and mean right auricular pressures were minimally above usually observed normal average values. However, these are within the normal ranges reported by some investigators.[18–21] Normal pressures in the right heart chambers and the pulmonary artery as reported by Fowler *et al.*,[22] based on their own findings and a review of those of other authors, were: for the pulmonary artery, 11–29/4–19 mm Hg, mean pressure 8 to 19 mm Hg; right ventricle 14–31.5/−0.5–+7 mm Hg; and right auricle mean −2 to +5 mm Hg.

Effect on Right Ventricular or Pulmonary Artery Pressures: Right ventricular systolic, or pulmonary artery systolic, diastolic and mean pressures were not affected by digitalis in the two groups of cases with the exception of case 3. The cause for the slight fall in the right ventricular systolic pressure in this case is not apparent. This patient did not have clinical evidence of heart disease. Since "pulmonary wedge" pressure was not measured, a decreased left ventricular reserve cannot be excluded. However, if this were due to left heart failure one would perhaps expect an increase in cardiac output after digitalization. In this instance there was a slight fall in cardiac output. The slight fall in pressure therefore may have been related to the decrease in cardiac output.

Effect on Venous Pressure: In 7 of the cases reported here in which successive peripheral venous pressure measurements were obtained, there were no significant decreases following digitalization. Dock and Tainter[23] and Katz *et al.*[24] showed that in dogs digitalis produced a fall in cardiac output due to its peripheral action. They found pooling of the blood in the viscera caused by constriction of hepatic veins. This action of digitalis has not been observed in man. A number of years ago Rytand[25] reported a fall in venous pressure in 8 normal subjects maximal at 24 to 32 hours after oral digitalization. Direct venous puncture using the Moritz-Tabora technique was employed. However, the fall was only 1.96 cm saline, and its significance therefore questionable. Stewart and Cohn[26] did not find any significant change in venous pressure in normal individuals by a method similar to Rytand's. In man, Harvey and her associates[10] postulated that "either there is no peripheral venous action of the drug, or that if there is such an effect, it is too small to be detected, is obscured by rapid reflex venous adjustments or does not influence central or right heart filling pressures."

Right Auricular Pressure and Right Ventricular End-Diastolic Pressure: Tendency of the right ventricular end-diastolic pressure to fall in two cases (cases 3 and 6) and the slight decrease in mean right auricular pressure in 5 of 6 cases in which it was measured may have been an effect of digitalis, though this cannot be stated with cer-

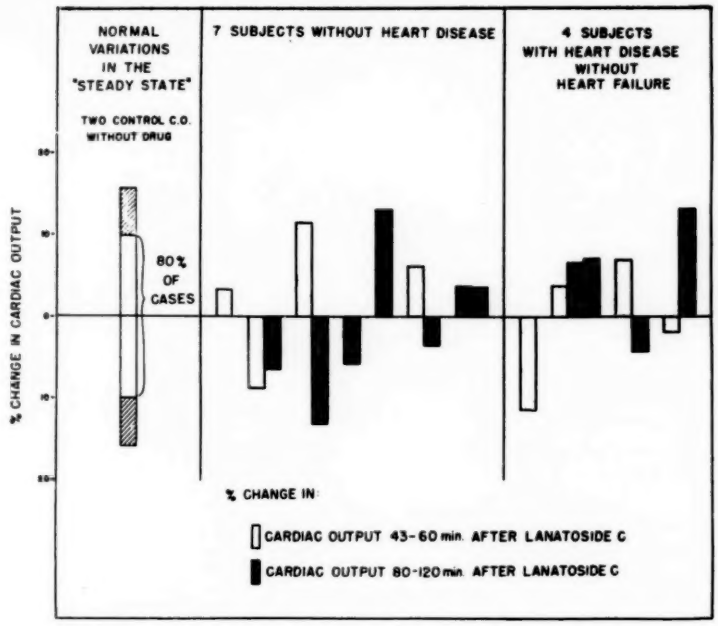
NORMAL VARIATIONS IN THE "STEADY STATE"
TWO CONTROL C.O. WITHOUT DRUG
7 SUBJECTS WITHOUT HEART DISEASE
4 SUBJECTS WITH HEART DISEASE WITHOUT HEART FAILURE
80% OF CASES
% CHANGE IN CARDIAC OUTPUT
% CHANGE IN:
CARDIAC OUTPUT 43-60 min. AFTER LANATOSIDE C
CARDIAC OUTPUT 80-120 min. AFTER LANATOSIDE C

FIG. 1. Effect of lanatoside C on cardiac output.

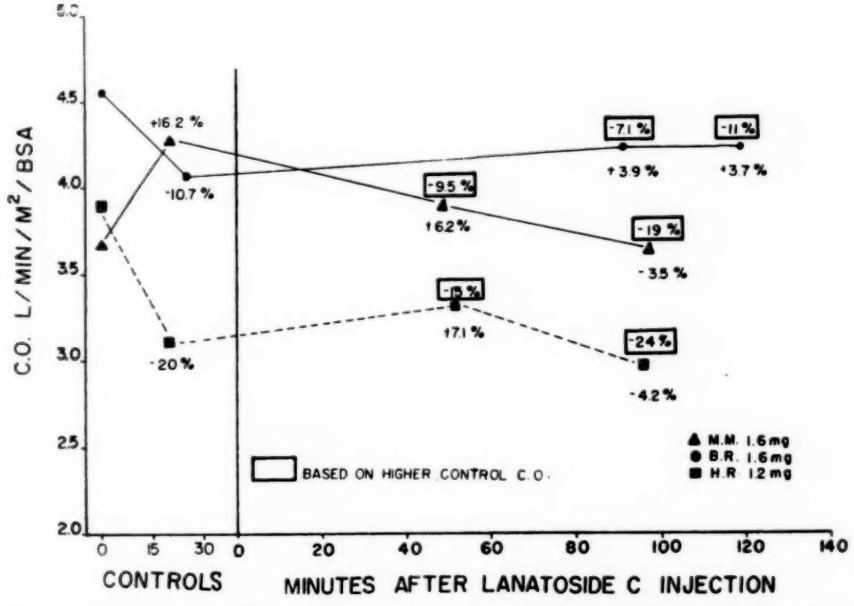

FIG. 2. Changes in cardiac output after lanatoside C in three patients, calculated from higher of two control cardiac indices. ▲ Case 6; ● case 7; ■ case 10.

tainty. The changes in the pressures were small and the changes in the end-diastolic pressure occurred in only 2 of 8 patients in which it was obtained. In normal dogs intravenous infusion of cardiac glycosides has been shown to increase the contractile force of the right ventricle.[27] This might account for better emptying and, therefore, a decrease in right ventricular end-diastolic pressure. A decrease in right auricular pressure was observed by McMichael and Sharpey-Schafer[9] following intravenous digoxin in three normal subjects studied by the technique of right heart catheterization. Cardiac output was also considered to have fallen. The fall in

right auricular pressure in these patients as well as in those with heart failure following digoxin led them to an impression that "the major benefits of digoxin treatment result from a peripheral action on venous pressure and not from any tonic or stimulating action on the heart."[9] However, this was not confirmed later by Ahmed *et al.*,[5] in the same kind of study with another cardiac glycoside, ouabain, nor by other investigators with the administration of digoxin[4,6,10] or Cedilanid.[12]

Effect on Cardiac Rate: Cardiac glycosides in subjects with normal hearts and patients with heart disease without heart failure may produce slight slowing in the heart rate or there may be no change.[5,6,9,11,12,26,28,29] In the present study lanatoside C did not cause a significant change in the heart rate.

Changes in Cardiac Output: Burwell *et al.*[28] in 1928 gave digitalis leaf orally in four normal subjects and made daily observations of cardiac output using a modification of the carbon dioxide method.[30] They found a decrease in cardiac output with a tendency to return toward normal when toxic levels were reached. Stewart and Cohn[26] in 1932, using the acetylene method of Grollman,[31] studied the effects of a single dose of oral digitalis (0.8 to 1.0 Gm) in normal individuals. A decrease in cardiac output and diminution of the heart size were described. The maximum effects were observed 4 to 24 hours after digitalis was given. Experiments in dogs have also shown a decrease in cardiac output following intravenous digitalization.[23,32–35] This decrease may be due to hepatic vein constriction which has not been demonstrated to occur in man. It is difficult to compare the indirect methods of cardiac output determinations with those done by direct methods. In addition the methods of digitalization and the times of observations were also different.

In acute studies in man with intravenous cardiac glycosides using the technique of right heart catheterization in subjects with normal hearts or diseased hearts which are not in failure, the cardiac outputs have been reported to decrease or show no change.[5–7,9–12] McMichael and Sharpey-Schafer[9] in three, Harvey *et al.*[10] in two, and Bing *et al.*[7] in seven subjects with normal hearts reported a decrease in cardiac output following administration of cardiac glycosides. However, Ahmed *et al.*[5] in nine individuals with normal hearts and Ferrer *et al.*[6] in two cases with slight degree of pulmonary hypertension without evidence of heart disease and in three patients with cor pulmonale without heart failure did not find any significant change in cardiac output after cardiac glycoside administration. In 12 patients with enlarged hearts who had no evidence of heart failure, Harvey *et al.*[10] reported a decrease in cardiac output in five, increase in one, and no change in six cases. Lagerlöf and Werkö,[11] in a series of seven patients with compensated heart disease, found no change in cardiac output following lanatoside C administration.

Interpretation of Cardiac Output Changes: In none of the 11 cases reported here was there a significant change in cardiac output following acute digitalization. The changes noted following digitalis administration were closely similar both in magnitude and distribution to the changes occurring in 71 cardiac catheterizations in patients not receiving medication who had two control resting cardiac output determinations under "steady state" conditions.[13] The true mean deviation for the control group and the group in the glycoside study was approximately zero. The average change in the glycoside group was 6.7 per cent compared to 5.7 per cent in the overall control study. Since 10 of the 11 cases had cardiac indices above 3.5 L/min/sq M BSA, controls with cardiac indices over 3.5 L/min/sq M BSA are used here for comparison. The average variation in the 11 cases was 6.6 per cent. Three (23 per cent) had changes in cardiac output greater than 10 per cent but less than 15 per cent. Twenty per cent of the controls showed the same variations. The greatest variation in this study was 13 per cent and in the control study it was 15.7 per cent.

The decrease in cardiac output after digitalis administration reported in the literature in subjects with normal hearts and patients with heart disease not in failure comes mostly perhaps from the lack of criteria to determine both the "steady state" and the significance of the changes observed. If our control study group is used for comparison, most of the cases reported in the literature would show no significant change.

Some variations in cardiac outputs after lanatoside C administration were shown in the presented data. As demonstrated in the cases with two control cardiac output determinations (see Fig. 2), the percentage changes from control levels after digitalization depended upon which control was used as the base line to measure the variation. If only one control output deter-

mination had been available, an error could easily have been made in interpretation in these cases. The oxygen consumption and/or the heart rate alone would not have been of help in these cases, since they were fairly constant. A decrease in A-V oxygen difference may be the only hemodynamic manifestation of anxiety.[36]

On the basis of statistical analysis of two successive cardiac output determinations in 20 control patients not receiving medication, Harvey and her associates[4] found that the cardiac outputs did not change more than ±9 per cent. Any change more than this value was considered significant. In a report from the same laboratory Cathcart *et al.*,[37] in a series of 100 catheterizations with two control determinations, found that 83 per cent varied less than 10 per cent, while 17 per cent of the cases showed greater deviations. In two cases there was a variation of greater than 15 per cent in cardiac outputs. In our series of 71 catheterizations, 80.3 per cent varied less than 10 per cent; only 2 or 2.8 per cent varied slightly more than 15 per cent. On the basis of the foregoing, 4 out of 5 cases reported to show a decreased cardiac output following digoxin by Harvey *et al.*[10] would not be considered significant. In two of their cases they found a decrease of 32 per cent and 21 per cent. In one of these cases the drop of 32 per cent was calculated 46 minutes after digitalis. In the same case, 20 minutes after digitalis the fall was 12 per cent, and 69 minutes later, at which time theoretically the more significant change should have occurred, there was only a decrease of 13 per cent. One normal subject had a fall of 18 per cent in cardiac output 20 minutes after digoxin; however, 75 minutes later the decrease was only 1.2 per cent.

McMichael and Sharpey-Schafer[9] reported a fall in cardiac output in three normal subjects following digoxin. In two instances, according to our criteria, the decrease would be considered significant. Ahmed *et al.*[5] later studied the effect of ouabain in nine normal subjects and could not find any significant change in cardiac output following administration of the drug. Two of these patients had changes in cardiac output greater than 15 per cent but in divergent directions. In both reports there are no data available regarding oxygen consumption and A-V difference.

Decrease in cardiac output after strophanthus was reported by Bing and his associates[7] in seven patients with normal hearts. In two of these cases there were changes in oxygen consumption from control levels of +80 cc and −133 cc. Since strophanthus is not known to cause such changes in oxygen consumption, these variations indicate changes in state in those patients during the study. Control cardiac indices in two other patients are far above the range considered to be basal. The narrow A-V oxygen difference suggests in these cases a state of anxiety.

Observations in the cases reported here and those cases reviewed in the literature, using our control group for comparison, strongly suggest that acute digitalization in patients with normal hearts and diseased nonfailing hearts does not produce a significant change in cardiac output. This suggests that lanatoside C either has no action on nonfailing hearts, or this action is not detectable by the methods used. The duration of the study may also be a factor. Observation may not have been long enough to obtain the optimum effect of the drug used. However, at least some effects should be expected during this period of observation if this is considered in light of the results obtained in patients with heart failure.[9–11] Unless the nonfailing myocardium responds at a different time, a one- to two-hour follow-up after acute digitalization would seem to be sufficient to observe any changes which may occur.

Changes in Systemic Blood Pressure: Several authors[5,6,10–12] have found either no change or some increase in systemic arterial blood pressure after acute digitalization in the types of patients under discussion. Harvey *et al.*[10] postulated a vasoconstrictor effect of digoxin on the arteriolar bed on the basis of no change or an increase in mean systemic pressure when there was no change or a fall in cardiac output. It is not unusual for compensatory vasoconstriction to occur in the presence of a fall in cardiac output. In the cases reported here, there was no significant change in cardiac output and in most instances the variations in systemic pressure following lanatoside C were observed prior to drug administration. In animals, toxic doses of digitalis have been demonstrated to cause a rise in blood pressure secondary to vasoconstriction.[38] This apparently results from a direct effect on the smooth muscles and partly from a central vasomotor stimulation. However, this was not found when average digitalizing doses were used.

Clinical Significance of Results: From the data presented, it has been shown that lanatoside C (and presumably the other cardiac glycosides as

well) in therapeutic doses does not seem to have any acute measurable deleterious effects on the hemodynamics of the cardiovascular system in subjects with normal hearts or cardiac patients not in heart failure. The problem of whether prophylactic digitalization is useful in patients with heart disease but not in heart failure is, however, not solved by this study. Nevertheless, it is felt that these patients can be digitalized without fear of decreasing cardiac output or producing unfavorable changes in blood pressure.

Summary

(1) The effect of acute digitalizing doses of lanatoside C on cardiovascular hemodynamics has been studied by the technique of right heart catheterization in 7 subjects with normal hearts and 4 patients with heart disease without clinical or hemodynamic evidence of heart failure.

(2) Lanatoside C in full therapeutic doses caused no significant changes in cardiac output, heart rate, systemic venous, right ventricular systolic, and pulmonary artery pressures. The systemic arterial pressures and resistances similarly were not appreciably affected. In 2 of 8 cases, there was a slight fall in the right ventricular end-diastolic pressure and in 5 of 6 cases there was a slight fall in right auricular pressure.

(3) Interpretations of the presented data were made on the basis of control studies. Difficulties in interpreting the changes in cardiac output in this type of study are emphasized.

(4) It would seem from this study that digitalis given prophylactically to patients with heart disease but not in failure would not have any deleterious effect on cardiovascular hemodynamics.

Acknowledgment

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Report on Therapy

Continuous Intramuscular-Drip Penicillin Therapy in Bacterial Endocarditis

A Reaffirmation*

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PENICILLIN remains the cornerstone of antibiotic therapy in streptococcal bacterial endocarditis.[1] Use of large doses of this drug, particularly when a resistant organism is encountered, has been a therapeutic approach well established by clinical and laboratory studies.[2] Maintenance of high serum penicillin levels has received considerable support,[2] although the method employed varies depending upon the investigator. Intermittent intramuscular aqueous procaine penicillin G, usually in combination with probenecid, is a frequently described regimen.[1,3] Finland *et al.*[4] have recently suggested that this basic program be augmented with intermittent and fairly rapid injections of sodium or potassium penicillin G. When massive doses of the drug are required, most authors have successfully employed continuous intravenous administration of penicillin, together with probenecid.[1,3]

During the early phases of the investigation into the use of penicillin in bacterial endocarditis, it was well established that continuous intramuscular-drip therapy provided blood levels comparable to those achieved by the intravenous approach and, indeed, possibly even higher.[5–7] The advantages to the patient were clearly described, and included almost complete freedom of activity and avoidance of venous trauma and phlebothrombosis, as well as the elimination of repeated painful injections. By changing the needle site, or by injecting procaine into the penicillin solution, it was possible to alleviate the mild or moderate local discomfort that occasionally occurred.

In recent years, penicillin therapy by continuous intramuscular drip has been virtually ignored. The method is occasionally mentioned in passing[2] but has not achieved status as one of the major useful means of administration. However, Bunn *et al.*[8] in 1954, found this form of therapy of great value and have continued its use to the present time.[9] According to this group, side effects are minimal and the penicillin blood levels obtained are more constant than those obtained when the drug is given by intravenous infusion.

CLINICAL EXPERIENCE

We have used the method of giving penicillin by continuous intramuscular drip in the treatment of a group of six patients with bacterial endocarditis. The required amount of crystalline penicillin G is dissolved in 500 ml of 0.9 per cent saline solution or 5 per cent glucose in water. A No. 20 needle, $1^1/_2$ inches long, is inserted at an angle of approximately 30 degrees into the muscles of the lateral thigh. The clysis location is alternated daily. The drip is usually continued throughout the day, although an interruption of up to two hours is often permitted. It is our practice to allow the patient to use the bathroom with the clysis in place and at such times the bottle is attached to a mobile infusion stand. Aside from occasional mild discomfort at the needle site and the rare stoppage of flow, no difficulties have been noted in our series. Assays of serum bactericidal activity in the same patient receiving massive doses of penicillin, by both continuous intramuscular and intravenous

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routes, were compared. By either method of administration, consistently high and entirely comparable serum levels of penicillin were maintained.[10]

Case Histories

Two brief case reports will serve to summarize our experience with this mode of therapy and will demonstrate its therapeutic benefits.

Case 1(SLH 293–580). This 45-year-old housewife was admitted on October 27, 1955, for the treatment of chronic congestive heart failure associated with mitral stenosis. The heart failure was difficult to control, and her hospitalization was prolonged by a period of anticoagulant therapy for recurrent pulmonary infarction. After five months of continuous hospitalization, a mitral commissurotomy was performed (March 21, 1956). One month later a fever developed, together with petechiae and splenomegaly. A species of enterococcus was cultured from the blood.

Aqueous procaine penicillin was started in a dose of 1 million units intramuscularly every six hours and was increased to 2 million units every four hours on the following day. Probenecid was given daily in a dose of 0.5 Gm every six hours. Sensitivity studies demonstrated penicillin and bacitracin to be the most effective antibiotics in terms of bactericidal action. For both drugs the bactericidal end point was 6.25 units per milliliter. Because of the patient's partial deafness, it was decided to start bacitracin rather than streptomycin, although the latter was added one week later. After a week of intermittent intramuscular therapy, during which time the temperature fell gradually, the patient was apathetic, despairing, and uncooperative. She refused further intermittent intramuscular therapy and rebelled at the prospect of an intravenous approach. Accordingly, a continuous intramuscular drip of 20 million units, and later 30 million units, of crystalline penicillin G daily was started.

Following the institution of this method of therapy, a striking improvement in effect was apparent. The patient again became friendly and cooperative and there was return of interest in her appearance and surroundings. During the five weeks of daily treatment with continuous intramuscular administration of penicillin she was virtually without complaint and she recovered uneventfully.

Bacitracin was discontinued after 25 days. On days 21 and 29 of treatment, the serum was bactericidal for the patient's organism in a 1:2 dilution and was bacteriostatic and slowly bactericidal from 1:4 through 1:64.

Case 2(SLH 319–575). This 13-year-old schoolboy underwent closure of an atrial septal defect on June 3, 1958. Two weeks postoperatively the temperature rose and the spleen was palpated 1 cm beneath the left costal margin. Hemolytic *Staphylococcus aureus*, coagulase negative, was cultured from the blood. Sensitivity studies demonstrated a bactericidal effect of penicillin at 12.5 units per milliliter, while the bactericidal level for erythromycin was 50 units per milliliter.

The patient fought intermittent intramuscular penicillin therapy and had to be restrained to receive medication. Since the temperature had fallen to normal after five days of penicillin, this drug was stopped and erythromycin given by mouth. Soon thereafter the temperature rose again and the patient was placed on 20 million units of crystalline penicillin G daily by continuous intravenous drip, together with probenecid, 0.5 Gm every 6 hours, and erythromycin. Attempts to insert the needle in the vein were vigorously opposed, and therefore the 20 million units of penicillin were given by continuous intramuscular drip. This approach was promptly accepted by the patient, and his recovery over the six weeks of therapy was characterized by his reasonable and cooperative attitude.

Summary

The effectiveness and ease of penicillin administration by continuous intramuscular drip has been re-emphasized. Its wider use is suggested in the treatment of those diseases in which large doses of penicillin are required.

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Experimental Study

Sensitization by Dihydrotachysterol (DHT) for Induction of Cardiac Lesions by Various Agents*

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IN A SERIES of previous publications we showed that, in rats, the oral administration of either sodium phosphate[1] or calcium acetate[2] qualitatively alters the cardiotoxic actions of certain steroid vitamin-D derivatives, such as dihydrotachysterol (DHT), so that an acute purulent myocarditis results. Furthermore, in rats simultaneously treated with comparatively small doses of DHT plus calcium acetate, the resulting cardiovascular lesions can be considerably aggravated by a variety of stressor agents—for example by cold baths, restraint, or noradrenalin.[2] On the other hand, pretreatment with similar doses of DHT alone did not suffice to render the cardiovascular system particularly stress-sensitive.[3] The production of an electrolyte-steroid-cardiopathy with necroses (ESCN) by combined treatment with certain corticoids and "sensitizing sodium salts" is likewise greatly enhanced by various stressors; indeed, corticoid conditioning alone suffices to so alter reactivity of the heart that it undergoes necrosis during exposure to stress.[3] All these observations show that suitable humoral conditioning with various steroids (hormones or vitamins) and electrolytes can selectively condition the cardiac muscle for the production of necroses by stress.

It is the object of this communication to report on experiments which indicate that intense acute overdosage with DHT alone, though not sufficient to produce cardiac necroses in itself, suffices to predispose the cardiac muscle to the production of necroses by cold or by papain, Plasmocid, noradrenalin, or vasopressin in doses themselves virtually ineffective.

MATERIAL AND METHODS

One hundred twenty female Sprague-Dawley rats, with an average initial body weight of 95 Gm (range 90–102 Gm), were subdivided into 12 equal groups, and treated as indicated in Table I.

Dihydrotachysterol (*DHT*) was administered by stomach tube in the form of a microcrystal suspension, at the dose of 150 mg in 0.5 ml of water, twice daily during the first two days and once on the third day.

TABLE I

Effect of Dihydrotachysterol upon the Potential Cardiotoxic Action of Various Agents

Group	Treatment	Cardiac necroses[a]	Mortality (%)
1	None	0	0
2	DHT	0.1 ± 0.10	0
3	Cold	0	0
4	Cold + DHT	1.2 ± 0.28	10
5	Papain	0.2 ± 0.15	0
6	Papain + DHT	2.3 ± 0.37	10
7	Plasmocid	0.1 ± 0.10	0
8	Plasmocid + DHT	2.6 ± 0.23	30
9	Noradrenalin	0.5 ± 0.17	0
10	Noradrenalin + DHT	1.6 ± 0.23	0
11	Vasopressin	0	0
12	Vasopressin + DHT	1.1 ± 0.38	0

[a] Intensity of cardiac lesions was assessed on a scale of 0–3; these figures are for the means of these determinations ± standard error.

* From the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montreal, Canada.

Exposure to *cold* consisted in the immersion of the rats in icy water, for a period of 3.5 minutes, twice during the second day.

Papain is a proteolytic enzyme contained in the dry latex of *Carica papaya*. Five grams of crude papain powder were added to 50 ml of distilled water; this turbid suspension was mixed in a Waring Blendor for ten minutes and then passed through a No. 40 Whatman filter paper; 0.2 ml of the resulting clear, amber-colored filtrate was injected into the jugular vein on the second day.

Plasmocid [8-(3-diethylaminopropylamino)-6-methoxyquinoline], 0.4 mg in 0.2 ml of water, was injected intraperitoneally three times during the second day.

Noradrenalin, 300 μg in 0.2 ml of oil, was administered subcutaneously twice on the second day.

Vasopressin, 10 i.u. in 1 ml of water, was injected subcutaneously twice on the second day.

Throughout the experiment all the animals were maintained on Purina Fox Chow. At the end of the third day, all surviving rats were killed with chloroform. The hearts were fixed in neutral Formalin for subsequent embedding in paraffin and histochemical determination of calcium with von Kóssa's technique. The intensity of the cardiac lesions was assessed in terms of an arbitrary scale of 0 to 3; the means of these determinations (with standard errors) are listed in Table I.

Results

As shown by the data in Table I, even at the high dose level at which it was given here, DHT did not produce any significant cardiac lesions during this acute three-day experiment (group 2). Among the other agents that we employed, papain and Plasmocid are known to produce widespread necroses in the myocardium, but only if they are given at higher dose levels. Cold, noradrenalin, and vasopressin rarely induce any extensive myocardial necroses, however, except in animals that are specially conditioned (e.g., by corticoids). In any event, in this series, the comparatively mild and brief treatment with cold (group 3), papain (group 5), Plasmocid (group 7), noradrenalin (group 9), or vasopressin (group 11) caused little or no histologically detectable cardiac damage. On the other hand, these same agents produced pronounced and often fatal cardiac necroses when they were administered concurrently with doses of DHT in themselves ineffective (groups 4, 6, 8, 10, and 12).

Histologic examination of the hearts revealed furthermore that, in the DHT-conditioned rat, the various additionally given agents produced histologic changes that simulated a much more severe DHT intoxication rather than the specific effects that would have been induced by higher doses of the eliciting agents themselves. For example, vasopressin, in itself, can produce minor cardiac lesions and, following corticoid conditioning, even extensive necroses, but it does not produce any lesions in the coronary arteries or calcification of the myocardium.[3] Yet, in group 12, in which vasopressin was administered conjointly with DHT, the latter in doses themselves ineffective, the resulting picture was typical of a severe DHT intoxication. Throughout the myocardium, the muscle fibers as well as the stroma between them became impregnated with von Kóssa-tingible calcium deposits (Fig. 1). The coronary arteries exhibited the Mönckeberg-sclerosis type of calcification, as well as an often very pronounced perivascular edema (Fig. 2).

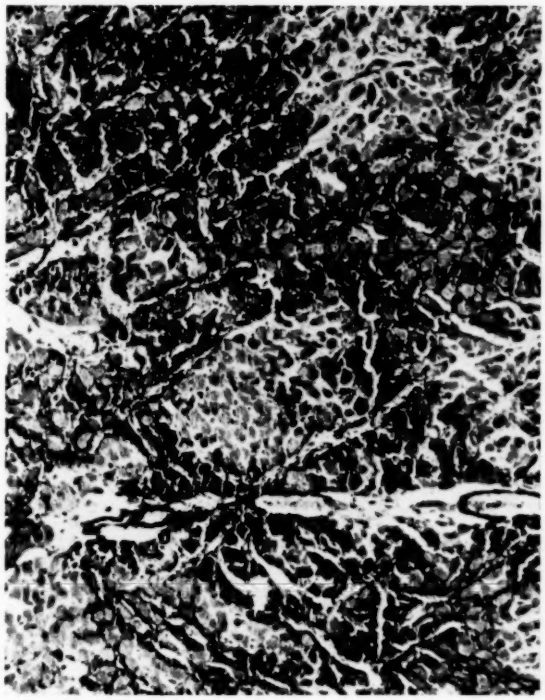

Fig. 1. Intense calcification of the coronary arteries and the myocardium in a rat of group 12 that was treated with vasopressin and DHT. In certain regions (*top*), calcification affects predominantly the stroma between the muscle fibers, while in other places (*bottom*), the entire muscle fibers are calcified. (von Kóssa; × 100)

Essentially similar changes were obtained in all the remaining groups in which DHT was administered in conjunction with another potentially cardiotoxic agent, yet the calcification was

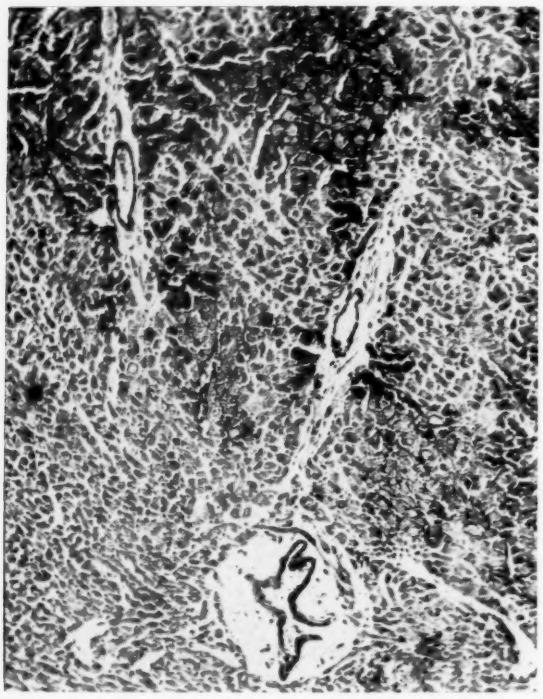

FIG. 2. Another region from the myocardium shown in Figure 1. Here, in addition to the calcium deposition, there is marked perivascular edema, especially around the largest of the coronary arterioles. (von Kóssa; × 75)

FIG. 3. Interstitial edema and inflammation without calcification, in the heart of a rat of group 4 treated with cold plus DHT. (von Kóssa; × 100)

not always equally pronounced. Often, in the same heart, certain regions were calcified; in others, the structural alterations consisted primarily of interstitial edema and inflammation, frequently accompanied by necrosis of muscle fibers (Fig. 3).

SUMMARY

Rats were treated, during three days, with doses of dihydrotachysterol (DHT) which, in themselves, caused no detectable cardiac lesions. In the hearts of these animals, necrosis, inflammation, and coronary calcification could be produced by various agents (cold, papain, Plasmocid, noradrenalin, vasopressin) which, in themselves, likewise produced no significant cardiac lesions under similar conditions of dosage.

After brief sensitization with small doses of DHT, even agents which normally have no tendency to produce coronary lesions or calcification of the myocardium (e.g., vasopressin) elicit these changes which are usually induced by more prolonged and intense treatment with DHT alone. Apparently, the potential cardiotoxic effect of mild DHT overdosage can be accentuated by a variety of nonspecific agents.

ACKNOWLEDGMENTS

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The authors gratefully acknowledge generous supplies of dihydrotachysterol (Calcamin) from Dr. A. Wander, S. A., of Plasmocid from The Lilly Research Laboratories, of noradrenalin from Sterling-Winthrop Research Institute, and of vasopressin (Pitressin) from Parke Davis and Company, Ltd.

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Seminar on Ballistocardiography*

Ballistocardiographic Studies on Athletes†

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THE STUDY of the ballistocardiograms of athletes has a unique contribution to make to the over-all understanding of ballistocardiography. Athletes are a special case in the more general BCG theory. Certain feats of skill, strength, and endurance are unique to them and require a degree of cardiovascular fitness and adaptability far beyond that ever envisioned by the average physician. It is therefore axiomatic that if a specific type of BCG is common to this group, it is the best type of BCG. If the athlete is a world champion his BCG, like his performance, becomes a standard against which all others may be compared.

Other athletic performances may require lesser degrees of cardiovascular fitness and depend more on strength alone or some other feature of physical efficiency. If the athletes in these groups display BCGs that differ significantly from those in the first group, a measurable determinant of the contribution of the cardiovascular system to the specific physical performance can be defined.

Additional information is available from the study of the BCGs of exathletes, of young students, of students undergoing serious physical conditioning for specific sports, and finally from the BCGs of older men undergoing physical rehabilitation through exercise.

It is the purpose of this communication to present and analyze the ballistocardiograms of these different groups and correlate the findings with physiologic concepts.

One of the important contributions ballistocardiographic research has made to human physiology is that it has revealed a correlation between myocardial force display during the cardiac cycle and a well-defined component of physical fitness, endurance. In order to explain the significance of this statement, it is pointed out that the exercise process is amenable to a threefold subanalysis in which physical performances are correlated with different physiologic systems:

Neuromotor *skill* reflects the integrative action of the *central nervous system.*

Strength is determined by morphologic features, more particularly by the bulk of *striated musculature.*

Endurance depends largely on the functional efficiency of the *cardiovascular system.*

Ballistocardiography is of little relevance regarding the first and second but has proved to be of supreme importance for the study of the third component.

A finding of general physiologic and clinical relevance that has been clarified through ballistocardiographic studies is that at rest the heart

* This issue contains Part X of the Seminar on Ballistocardiography (edited by Sidney R. Arbeit, M.D., F.A.C.C.). A schedule of the articles already published in this seminar may be found on pp. 101–102 of the January, 1959, issue (Vol. III, No. 1). Parts XI to XIII are scheduled as follows: *Part XI*—Comparison of Ballistocardiographic Systems with Special Reference to the Use of a Jerkmeter (J. E. SMITH and H. L. RIEGHARD (August, 1959, issue). *Part XII*—Ballistocardiogram in Functional Heart Disease, NAHUM J. WINER (September). *Part XIII*—A Clinician's Approach to the Ballistocardiogram, EDWARD W. BIXBY, JR., *and* Summary and Conclusions, SIDNEY R. ARBEIT (October).

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This review is based on material published from our laboratory during the past several years. Members of the group participating in these studies include Sidney R. Arbeit, Wm. E. McCubbin, Aarni Koskela, Sirkka-Liisa Hilkemaa and Peter Jokl. Dolores Little performed the statistical analyses.

The investigations were supported by the Research Fund Committee of the University of Kentucky, to whom the author expresses his indebtedness.

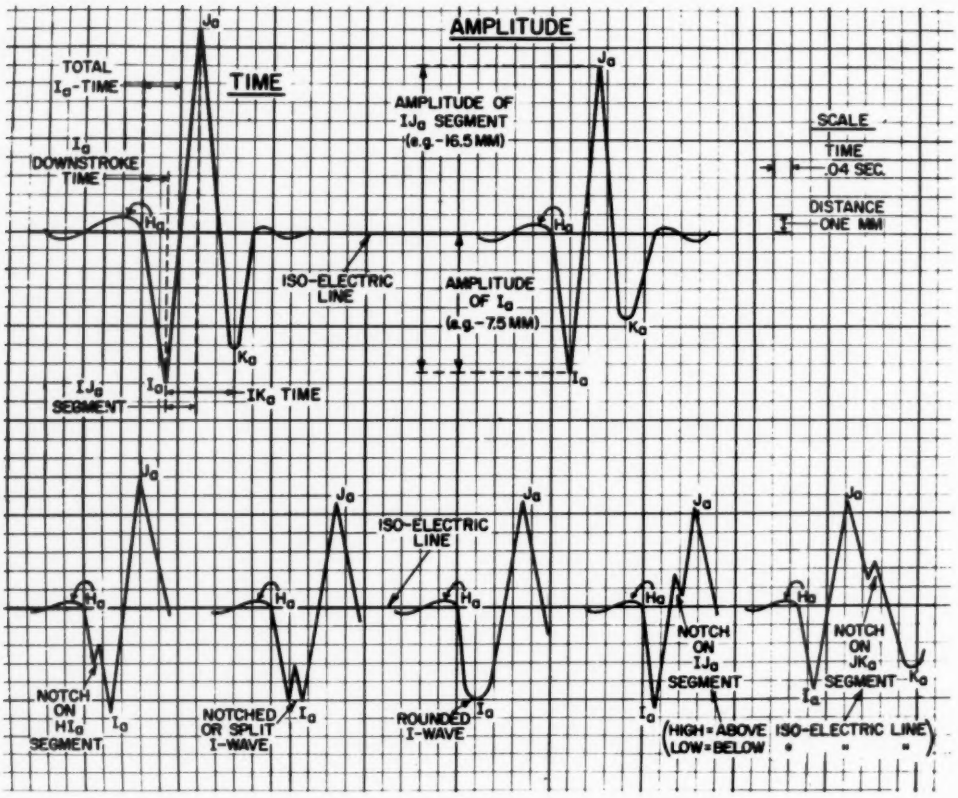

FIG. 1. Measurement of time and amplitude characteristics of normal ballistocardiogram. (From Arbeit, S. R., *et al.*: *Am. Heart J.* 54: 556, 1957; reproduced by permission of the authors and the C. V. Mosby Co.)

of highly trained track athletes, whose endurance is far greater than that of untrained young men, applies greater force than does the heart of the latter; and that the athletes' resting bradycardia is associated with superior kinetic potential as revealed during systole.

Figure 1 explains the two main principles for the quantitative evaluation of the normal ballistocardiogram in terms of amplitude and time variants of the systolic complex. Figure 2 illustrates the various grades of BCG abnormality.

Size of Heart and Kymographic and Ballistocardiographic Amplitudes During Systole

The size of the heart of the majority of champion athletes who are endowed with great endurance is well above average. However, the myocardium of such large hearts is not hypertrophied, or only slightly so. The marked cardiac hypertrophy often seen clinically in advanced heart disease is never encountered in athletes. A pathologically hypertrophied heart,

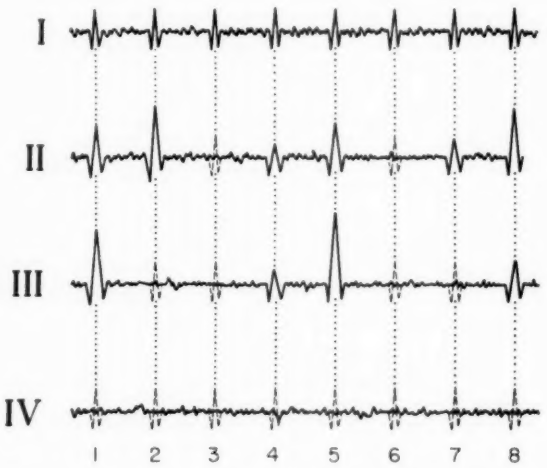

FIG. 2. Grade classification of ballistocardiograms; increasing degree of abnormality from grade I to grade IV.

even if it is not enlarged, may weigh much more than a well-trained athlete's heart of much greater size.

Roentgenkymography of such hearts at rest

shows very small marginal contraction amplitudes of the left ventricle, simulating the picture seen in myocardial disease. However, large systolic excursions are easily induced by exercise, though the heart becomes smaller in size during the effort.

Are diminution in cardiac size and amplification of kymographic pulsations during exercise accompanied by an increase of ballistocardiographic amplitudes? Is a heart thus adapted to the short-term requirements of the physiologic demands under reference capable of releasing greater contractile forces? These questions can be answered in the affirmative. In a series of studies of one of the best United States long-distance runners, the characteristic reduction in size of the heart after a race was found to be accompanied by a marked increase in the amplitudes of the IJK complexes.[3]

FIG. 3. Ten ballistocardiograms from young, healthy, athletically untrained male university students.

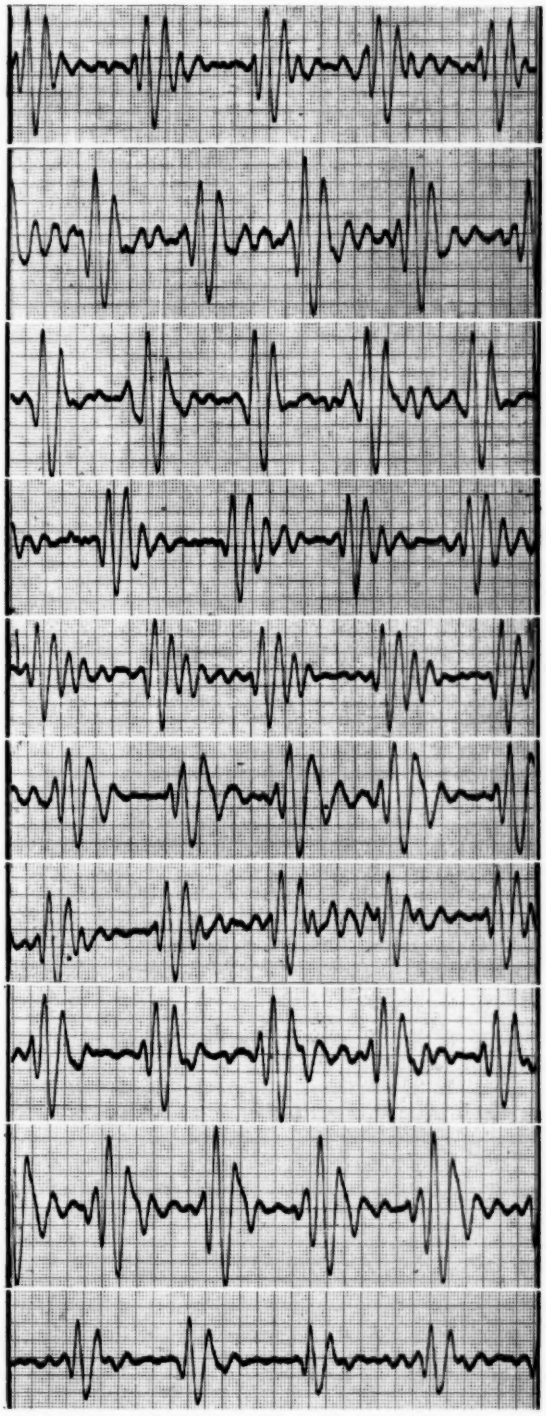

FIG. 4. Ten ballistocardiograms from track running champions.

Comparison of BCGs of Athletes, Nonathletes, and Exathletes

Three series of ballistocardiograms are presented in Figures 3-5 with a view to demonstrating the nature of the relationship between different levels of physical efficiency and corresponding variants of cardiac force display. The first series of tracings was taken from young, healthy, athletically untrained male students (Fig. 3); the second from participants at the NCAA track championships at Austin, Texas, in 1957 (Fig. 4); and the third from former Olympic and national champions who had discontinued their training for 20 or more years (Fig. 5).

SELECTION OF SAMPLES

Nonathletes: The BCGs in Figure 3, taken from young, healthy, athletically untrained male students, were selected from a consecutive series in accordance with the correspondence of their time and amplitude characteristics with the norms established at our laboratory.[1]

Athletes: The BCGs in Figure 4 were taken at the NCAA championships at Austin, Texas, in 1957 from all participants in the running events. Each man's best performance was computed according to the scales of the International 1000 Point Table. The BCGs from the ten most outstanding subjects were chosen for analysis. The extraordinary performance capacity of these men is indicated by the fact that none of them rated below 1000 points; this, therefore, is probably the most exceptional group of athletes ever subjected to a cardiovascular study.

Exathletes: The BCGs in Figure 5 were taken from men who during their twenties and thirties had been outstanding athletes. Their performances then corre-

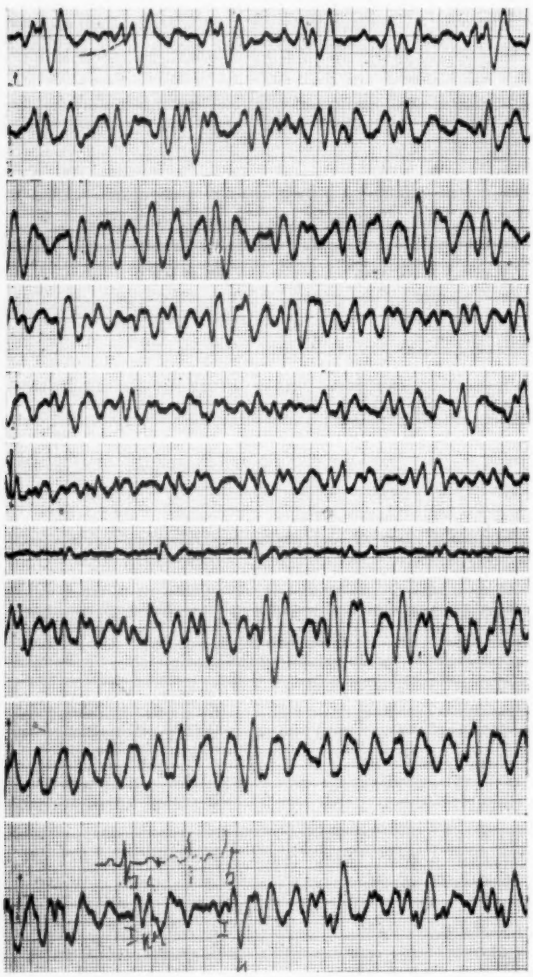

Fig. 5. Ten ballistocardiograms from former champion athletes after prolonged periods of physical inactivity.

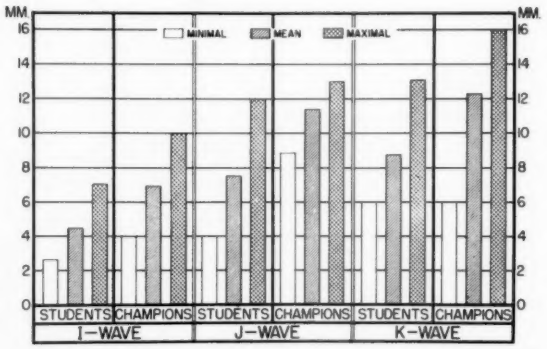

Fig. 6. Subanalysis of amplitude measurements of IJK complexes of standardized velocity ballistocardiograms of young, healthy students and of track champions (minimal, mean, and maximal values computed from each tracing).

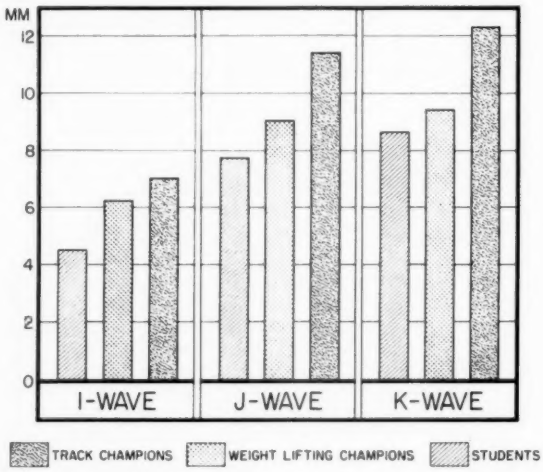

Fig. 7. Comparative amplitude analysis of I, J, and K waves of standardized direct-body contact velocity ballistocardiograms of ten champion track runners, 10 champion weight lifters, and 10 young healthy students.

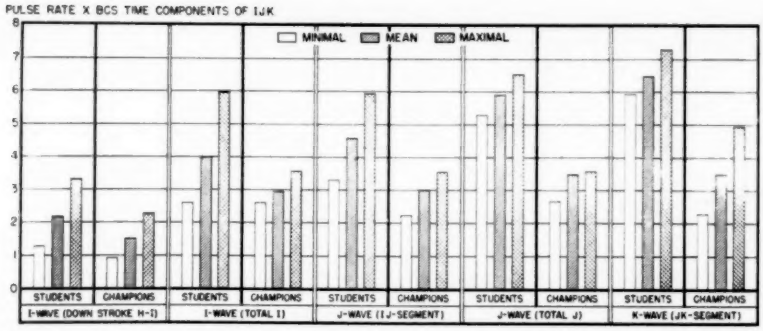

FIG. 8. Comparison of quotient (mean pulse rate × time fractions of IJK complex) computed for students and for track champions. The time segment occupied by the systole in each cardiac revolution is proportionately smaller in the ballistocardiograms of the athletes than it is in the tracings obtained from the students. The magnitude of the differences is represented by the respective sizes of the vertical columns for the 5 comparative analyses.

sponded to those of the subjects whose tracings are reproduced in Figure 4. Among them are three Olympic winners, an All-American football end, and three NCAA champions. All discontinued their training 20 or more years ago.

Thus, in selecting each of the 10 tracings in the above three groups, a twofold principle was applied. First, that of evaluating the athletic performances of the men at the time of their prime, in accordance with the criteria detailed above. Secondly, that of stipulating for group III a long period of inactivity following their years of intensive training.

INTERPRETATION OF BALLISTOCARDIOGRAMS

The tracings from the series of the athletes and of the students differ quantitatively; mean resting pulse rates were 45 as against 66; amplitudes of I waves measured 7.1 vs. 4.5 mm; of J, 11.5 vs. 7.7 mm; and of K, 12.3 vs. 8.7 mm (Figs. 6 and 7).

When IJK times were related to the duration of the diastole, considerable variations became evident. As Figure 8 indicates, a much smaller fraction of each cardiac cycle of the athletes is taken up by the systole. The diastolic interval is therefore even longer than is immediately apparent on account of the bradycardia (Fig. 8).

The BCGs from Group III (exathletes) reveal a tendency toward disintegration of the normal pattern. Most of these tracings are no longer amenable to a quantitative analysis. Figures 5 and 9 detail the nature and variety of the disintegrative process.

The analysis of the above three series of BCGs is relevant for two reasons. First of all, it specifies quantitative differences of great significance between the BCGs of young, healthy, untrained subjects on the one hand and of outstanding ath-

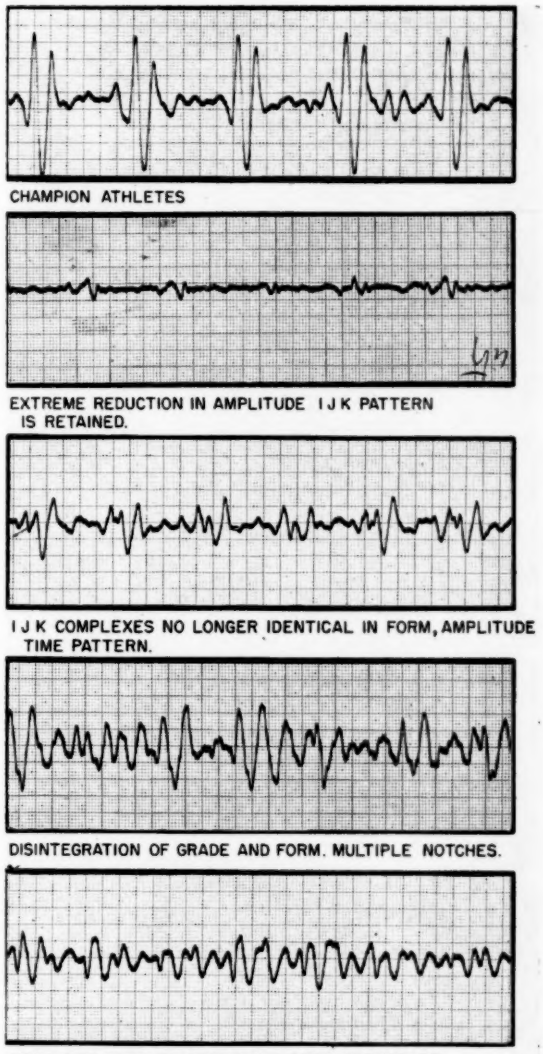
CHAMPION ATHLETES
EXTREME REDUCTION IN AMPLITUDE IJK PATTERN IS RETAINED.
IJK COMPLEXES NO LONGER IDENTICAL IN FORM, AMPLITUDE TIME PATTERN.
DISINTEGRATION OF GRADE AND FORM. MULTIPLE NOTCHES.
COMPLETE LOSS OF GRADE AND FORM STRUCTURE.

FIG. 9. Patterns of disintegration of ballistocardiographic grade quality from optimal class (top tracing) in former athletic champions after 20 and more years of inactivity

letes on the other. A measurable cardiologic characteristic is thus shown to be correlated to well-defined components of physical efficiency. The assertion previously made by us that ballistocardiography reflects levels of cardiovascular fitness within the range of the physiologic norm is well substantiated.

The differences between the ballistocardiograms of the track athletes and of the students are the result of the former's training. It would be impossible to find among any group of individuals other than that of champion runners so many BCGs like those in Figure 4. Functionally, each of the athletes in this sample is so exceptional that not more than one person in a million of the total population is likely to possess a physical performance capacity of comparable magnitude.

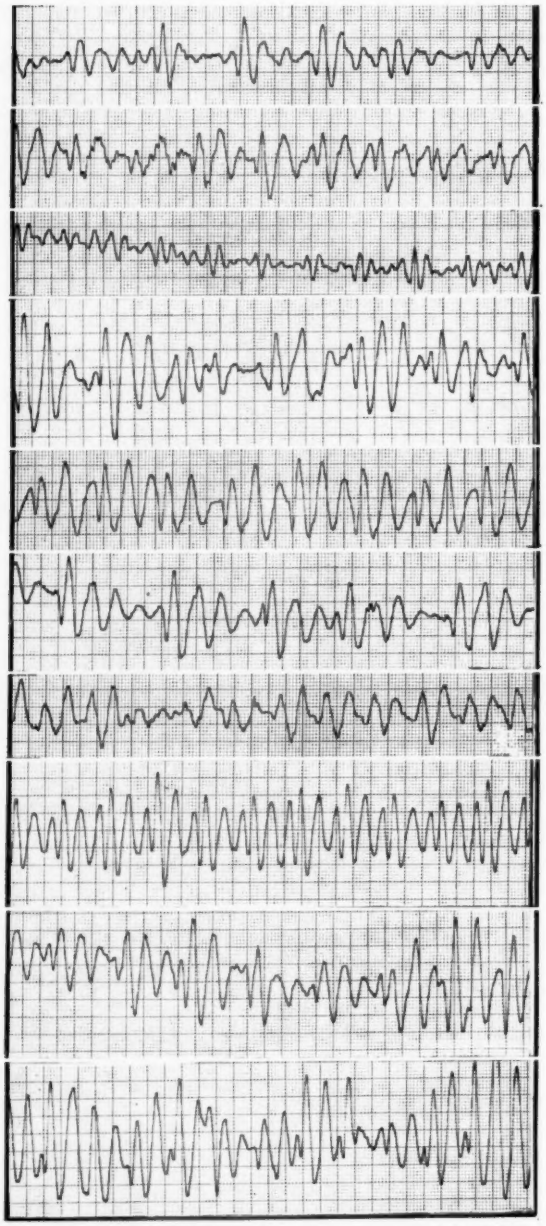

FIG. 10. Ten ballistocardiograms from weight lifting champions.

Second, the demonstration of distinct qualitative differences in BCG patterns between series II (athletes) and III (exathletes) corroborates clinical experiences to the effect that discontinuation of training is followed invariably by a decline of physical efficiency; this in turn is accompanied by a loss of BCG quality. The BCGs of the champions of 20 years ago suggest that a process of functional recession of the heart is induced by prolonged inactivity.

This process is reversible.

WEIGHT-LIFTING CHAMPIONS

The next group of athletes to be investigated were the weight lifters. Performance of this sport requires a maximum emphasis on *strength* (muscle bulk) and a moderate development of neuromotor *skill*. But there is little need for endurance per se in the process of lifting a weight and there is therefore small dependence on maximal functional efficiency of the cardiovascular system. This led to an interesting set of BCG findings.

BCGs were also taken from 10 of the greatest weight lifters of our time, among them several Olympic and national champions (Fig. 10). Their tracings differ from those of the track champions as well as from those of the students. Most of them allow identification of IJK complexes and therefore cannot be considered pathologic. But if it is recalled that ballistocardiography is capable of differentiating between normal variants of cardiac efficiency, the majority of the tracings of the weight-lifting champions reveal functional limitations. Amplitudes of systolic deflections vary considerably with respiration, in several instances by more than 50 per cent, a finding not often encountered even in untrained men of corresponding age. Also, amplitude fluctuations do not always follow the respiratory cycle. Furthermore, IJK patterns alter within short systolic sequences, so much so that it was at times difficult to analyze the tracings quantitatively in accordance with the principles detailed in Figure 1. To the meas-

urements in Figure 10, therefore, an element of arbitrariness is attached, in contrast to Figure 6, which precisely reflects patterns of cardiac force display of the hearts of the track champions and of the students.

FUNCTIONAL DIFFERENTIATION

It has frequently been claimed that weight lifting exerts a deleterious effect upon the normal myocardium. According to the criteria of BCG evaluation detailed in previous communications from our laboratory, the cardiovascular system of the 10 champion weight lifters is on the whole functionally inferior to that of the track runners—but, with one exception, not abnormal.

Now, weight-lifting training is an essential component of basic physical conditioning. Track runners and swimmers, football players and gymnasts, in fact the majority of men and women who prepare themselves for competitive sports, have found that in order to attain optimal performance levels they have to induce muscular hypertrophy by including in their training resistance work of one kind or another. By doing so, they not only benefit from the increased power of their musculature, but also from the metabolic aid thus made available. Apparently, there is an optimal physiologic state of muscular hypertrophy attainable through weight training. Beyond this, a decline of endurance will make itself felt, although further increases in strength may be induced by using resistance training ad maximum—as in the case of the weight-lifting champions. The latter are invariably very strong but may have rather limited powers of physical endurance. The great track athletes whose ballistocardiograms reveal such a unique standard of functional efficiency are less strong but capable of extraordinary performances of endurance. This precise characterization of the physical performance category under reference is very important because it indicates the kind of physical training which will induce the cardiac adjustment under review. Such training must incorporate both speed and staying power.

EFFECT OF SOFT-TISSUE LAYER UPON DIRECT-BODY BCG

Of all athletes, weight lifters possess the stoutest physiques. It is therefore appropriate to ask whether their thick soft-tissue layers exert an influence upon grade and form of direct-body ballistocardiograms.

The extent to which weight lifters differ in body bulk was demonstrated by a comparison of body indices from decathlon men, marathon runners, and weight lifters. Body indices were calculated by multiplying each man's weight by 100 and dividing it by the square root of his height. Thus a ratio is obtained which expresses individual "thickness." The validity of this measurement for the evaluation of constitutional features of the kind under consideration has been demonstrated in previous studies.

Although the weight lifters as a group are distinguished by conspicuously high body indices, many of them range close to the upper quartile of the field of normal distribution. The ratios of 10 among 17 weight lifters from whom we took BCGs are scattered between body-index levels 225–265. Into the same area of distribution, however, fall the corresponding figures for several decathlon men and even for some of the marathon runners; e.g., the cluster of body indices around athletic performance placement levels 13–15 is virtually of the same magnitude for the decathlon men, weight lifters, and marathon runners. Still, ballistocardiographically the weight lifters' tracings were unusual, even within this small sample.

If thickness of soft body tissue layers were a determining cause of grade and form deviations of the body direct-body ballistocardiogram, subjects with high indices would show common ballistocardiographic characteristics. This, however, is not the case. We had an opportunity of taking tracings from 8 men—none of them a weight lifter—over 260 pounds of weight. Five of them had grade I BCGs.

Contrary to what is widely assumed, thickness of soft body tissue layers does not seem to exert a decisive influence upon grade and form of the direct body acceleration BCG. For reasons not now discussed, factors related to thickness of soft body tissue layers other than mechanical ones, may in stout subjects exert an influence upon grade and form of the BCG. Such a conclusion is in fact suggested by subanalysis of the marathon data.

There remains the remarkable fact that the upper limits of human strength can be reached without the functional support of a heart optimally adapted to the demands of sustained effort. It is quite probable that the hearts of the weight-lifting champions possess other qualities of excellence that are not demonstrable ballistocardiographically. For example, weight lifting involves a Valsalva effect of unparalleled magnitude. Compared with this performance, the customary clinical tests designed to assess circulatory response to an acute rise of intrathoracic pressure (e.g., holding an expiratory resistance level of 20–40 mm Hg for 20–30 seconds) is a very minor stress.

BCG Changes During a 30-Day Physical Training Period

Four direct-body acceleration ballistocardiograms were obtained from a man, aged 40 years, who for a period of 30 days underwent a physi-

cal conditioning course.[2] When first seen, he was free of serious illness, although his physical performance was poor. An activity program was elaborated for him, consisting of daily 90-minute training periods of calisthenic exercises, apparatus gymnastics, weight lifting, and swimming. In the beginning, the calisthenic exercises had to be interrupted every two minutes to give the subject time to "recapture his breath." On the high horizontal bar he could perform one pull-up. He lifted only 20 pounds, repeating the effort up to ten times. He swam not more than three lengths in the standard-size (75 × 42 feet) swimming pool.

After the 30-day training period, he went through an uninterrupted sequence of calisthenic exercises of 10 minutes' duration, did eight pull-ups on the horizontal bar, and performed a number of movements on the parallel bars and the side horse which he had been unable to do four weeks earlier, lifted 80 pounds twenty times in succession, and swam 12 full lengths in the pool.

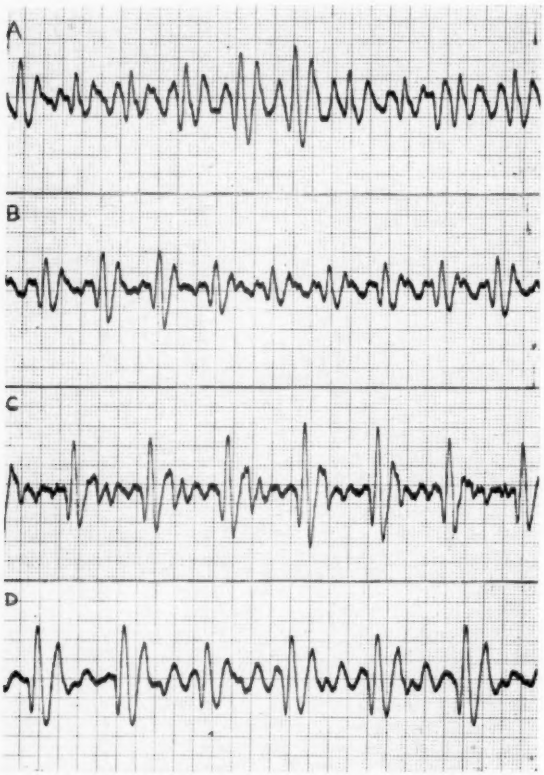

FIG. 11. Four direct-body acceleration ballistocardiograms from a 40-year-old man before, during, and after a physical conditioning course lasting 30 days. (A) Before experiment; (B) after 10 days of training; (C) after 20 days of training; (D) at end of 30 days. (From Arbeit, S. R., *et al.: Am. Heart J.* 54: 556, 1957; reproduced by permission of the authors and the C. V. Mosby Co.)

All tracings in Figure 11 are direct-body acceleration ballistocardiograms. The first was taken before the experiment; the second after the first 10-day training period; the third after 20 days; and the fourth at the end of 30 days. All tracings are grade I. Therefore, we are dealing with a functionally normal heart.

A number of features of the grade I tracings varied with the subject's changing state of physical fitness. Thus, we can assess cardiovascular efficiency with the range of the physiologic norm. The initial tracing (Fig. 11*A*) reflects functional normality, because every systolic contraction can be identified; because the three main waves, I, J, and K, are present throughout; and because the ballistic complexes are repetitive. In terms of efficiency, however, the tracing is only of "medium" quality, because there is tachycardia at rest; because the difference in amplitudes of the largest and the smallest IJK complexes is greater than 50 per cent; and because the form pattern of the complexes changes significantly with respiration and presumably also with diastolic influx of blood into the heart. We mention without comment at this stage that notching is present on several JK strokes.

In the second tracing (Fig. 11*B*) systolic deflections are more distinct as compared with Figure 11A; the difference between amplitudes of the largest and smallest IJK complexes is less marked; and the force pattern remains more identical throughout. No notching can be seen on JK.

In the third tracing (Fig. 11*C*) pulse rate at rest is again slower. Cardiac contractions are very regular and of considerable strength, and amplitudes of systolic complexes do not alter appreciably.

The fourth tracing (Fig. 11*D*) reveals a further slowing of pulse rate at rest, which now is around 65, as compared to 105 four weeks earlier. Mean amplitudes of IJ and JK are lower at rest. The significance of this observation will be detailed presently. Finally, the percentage scope of the differences of extreme amplitude deviations of the systolic deflections is small compared with corresponding findings in the beginning of the training period.

Obviously, ballistocardiography reflects different degrees of physical fitness in healthy subjects and allows a quantitative evaluation of the functional improvements induced by physical training.

Stress Resistance: The Marathon and Decathlon

We have taken ballistocardiograms from all participants in a marathon race in 1953 (Fig. 12), and the 1956 National Decathlon Championships and Olympic Trials at Wabash College, Crawfordsville, Indiana (Fig. 13). The

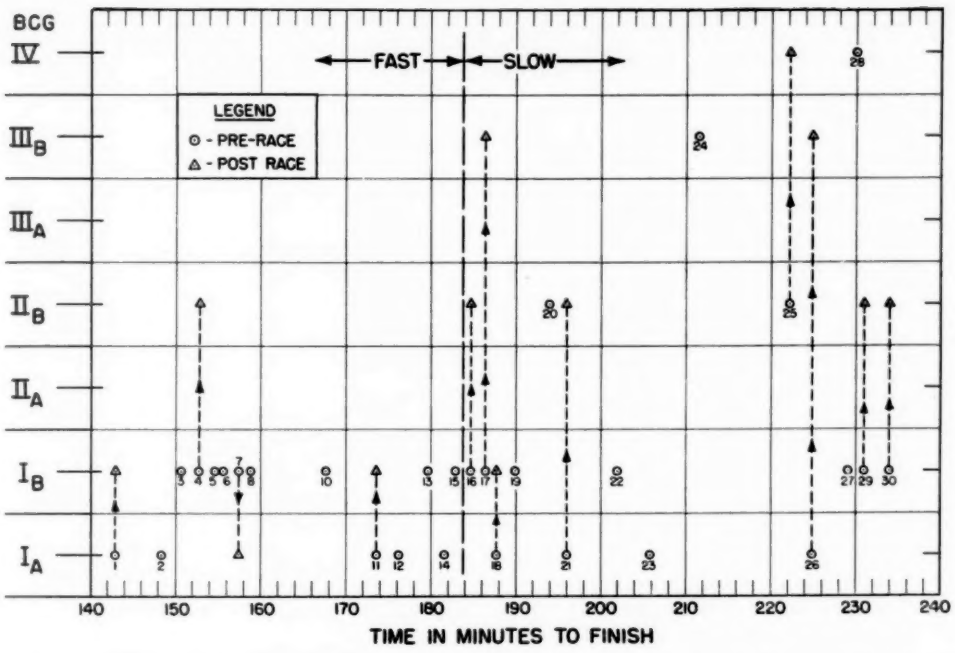

FIG. 12. Ballistocardiographic grade evaluation of 30 participants before and after marathon race, plotted according to placement. The ordinate indicates grade levels; the abscissa, running times. Circles show pre-race; triangles, post-race levels of ballistocardiographic grading. The interrupted vertical line between 180 and 190 minutes divides the "faster" from the "slower" runners. The differences between the ballistocardiographic grades of the "faster" as against the "slower" runners are striking. With one exception, all fast runners rated I. Such fluctuations as did occur during the race were insignificant in 14 out of the 15 men in the group. The "slower" runners present a more varied picture in which all ballistocardiographic grades are represented. Out of the 15 "slow" runners, 8 showed deterioration of ballistocardiographic tracings after the race; another 2 started and ended with III and IV gradings, respectively.

performances of the athletes were recorded and the results correlated. The most important lesson we learned from these two studies is that the stress resistance of the hearts of the majority of men is enormous. To amplify this statement it seems appropriate to point to the magnitude of the physical efforts involved in a marathon race and in a decathlon competition. In current clinical literature the terms "exercise" and "physical effort" are usually applied in a casual manner, comparable perhaps to the haphazard way in which the diagnostic entity "fever" was used 150 years ago. In a few instances attempts have been made to measure muscular performances, e.g., in connection with Master's two-step or Knipping's ergospirometric tests. But compared with the athletic feats under consideration, the amount of effort involved in these tests is negligible. In its reaction to the demands of muscular exercise, the normal myocardium is

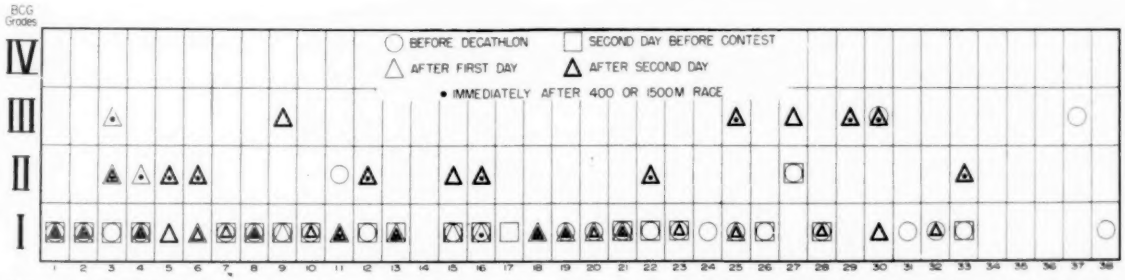

FIG. 13. Ballistocardiographic grade evaluation from participants in 1956 U. S. Decathlon championships at Crawfordsville, Indiana.

TABLE I
Body Type as Determinator of Ballistocardiographic Grading

	Total No.	Grade							
		I		II		III		IV	
		A[a]	B[b]	A	B	A	B	A	B
Leptosome	6	6	6	0	0	0	0	0	0
"Athletic"	18	16	11	2	5	0	2	0	0
Pyknic	6	3	1	2	1	0	2	1	2
TOTAL	30	25	18	4	6	0	4	1	2

[a] At rest and [b] after exhaustive physical effort (marathon race).

astonishingly stable. A few exceptions from the normal average pattern are shown in Figures 12 and 13. However, most of them concern short-lasting declines in grade rating of ballistocardiograms after maximal exertion. The significance of these observations cannot yet be fully evaluated.

Two men with BCGs of grades III and IV at rest participated in and finished the marathon race (see Fig. 12). Such observations seem to be of far-reaching importance. They suggest that extracardiac resources can make decisive functional contributions to the maintenance of an effectively elevated oxygen intake and metabolic balance, both prerequisites for long-distance running performances of the kind under study.

SUBANALYSIS OF MARATHON DATA

In the marathon study we correlated body types, running times, and ballistocardiographic grades of the participants before and after the race. Kretschmer's classification into asthenic or leptosome, athletic and pyknic types was used. The results of this investigation are summarized in Table I and Figure 12. Three observations are noteworthy:

First, that the 15 best runners' BCGs were of grade I before as well as after the race, with one exception, in which a grade II rating was found at the conclusion of the competition. Among the 15 less successful runners, all four ballistocardiographic grade levels were represented. In several instances there was a decline in quality of the tracings after the race.

Second, the asthenic or leptosome runners as a group ran "best," the pyknic runners as a group "worst." The "athletic" types ranked in between. However, the significance of the correlation under reference was not such as to have predictive value regarding *individual* performance. Also, it must be remembered that even the "worst" runners *completed* the 25-mile running race, a feat of which only a few hundred persons in the entire United States are capable. The question of running times in the marathon race is therefore of limited importance, although the ballistocardiographic differences between the "good" and the "bad" runners are most interesting from the physiologic point of view.

Third, there is the fact that among the asthenic or leptosome marathon runners no ballistocardiographic grades other than grade I were found before as well as after the race. Among the pyknic athletes, however, only one man started and finished the race with a grade I ballistocardiogram, while low-grade III and IV tracings were repeatedly encountered, among them several declines in BCG quality after the competition. This finding raises many questions. The prevalent idea that "fat old men" cannot run long distances is evidently not correct. True, none among the pyknic athletes ran "well," but they all completed the marathon race, quite an extraordinary feat, considering current clinical standards of assessment of physical efficiency. That the myocardium of some of the runners was "poor" in accordance with accepted histopathologic criteria can be taken for granted. A grade III and IV ballistocardiogram indicates a degree of functional impairment of the heart muscle so great that the assumption of morphologic abnormalities is fully justified. But there were among the runners no clinical signs or symptoms of cardiovascular distress or disease after the race. None of them suffered any damage.

We have on previous occasions drawn attention to the impressive discrepancy between high levels of physical efficiency, on the one hand, and the presence of cardiovascular abnormalities, on the other, as revealed by clinical and pathologic studies in athletes. With the intro-

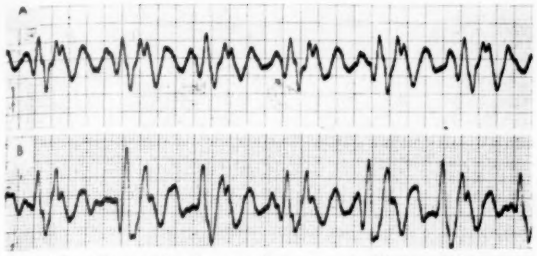

FIG. 14. Direct-body acceleration ballistocardiograms from world record holder in the Decathlon, taken during Decathlon championships. In four of the seven systolic deflections in (B) I waves are absent. In the remaining three complexes I waves are present. Otherwise, the tracings are normal. J and K waves are in evidence throughout. There is distinct repetitiveness. Variations of amplitudes are within physiological limits. There are notches on JK. (A) was taken one day earlier and IJK waves are recognizable in every systolic complex. Pulse rate is 62, same as in record (B). Amplitudes are smaller. The notches on JK represent a constant characteristic of the athlete's ballistocardiogram.

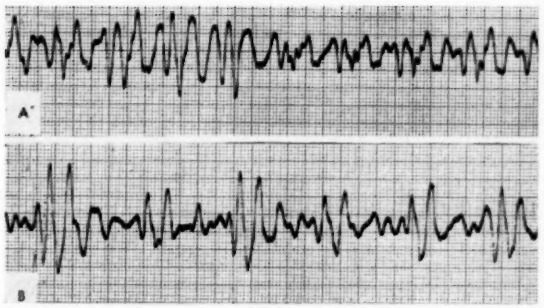

FIG. 15. Acceleration ballistocardiogram from double Olympic winner in pole vaulting, U. S. champion in Decathlon. (A) Tracing was obtained after the 400-meter race at the end of the first day of the U. S. Decathlon Championships. The normal IJK formation is lost for a time sequence equivalent to several consecutive systolic contractions. (B) Normal tracing taken from same athlete on the next day at rest.

duction of ballistocardiography, the issue under reference has become amenable to further clarification.

BCG Case Observations in Champion Athletes

We have seen very few exceptions to the rule that first-class sportsmen retain their normal ballistocardiographic pattern after athletic competitions. One of the greatest decathlon men of the world developed temporary absence of I waves after the 1500-meter race at the end of a championship contest (Fig. 14); a few missed systolic deflections were seen in the BCG of an Olympic champion after the 400-meter race at the conclusion of the first day's contest of the decathlon (Fig. 15); and there were abnormalities seen at rest as well as after competition in the BCGs taken from the strongest man in the world, record holder and Olympic champion in weight lifting. In this case, however, constitutional factors seemed to explain the pathogenesis of the cardiac abnormality and no cause-and-effect relationship with this athlete's strenuous physical activities could be established.

How can an individual display such extraordinary physical efficiency without being able to rely on the functional support of a normal heart? Several such cases are on record.

In a participant in the 1952 Olympic Winter Games, U. S. (50-km ski running and jumping 271 ft), with a history of a wartime injury from bullets x-ray examination revealed a piece of metal embedded between the pericardium and the base of pulmonary artery. In a long-distance runner of international repute a routine fluoroscopic examination revealed a large aortic aneurysm.

We have recently conducted extensive tests on a young woman with tetralogy of Fallot. At surgery, Blalock established a communication between the subclavian and pulmonary arteries. After the operation the girl, still cyanotic even at rest, took up swimming and attained success in competitive contests. We reproduce two acceleration BCGs taken before and after a 100-yard breaststroke race (Fig. 16A and

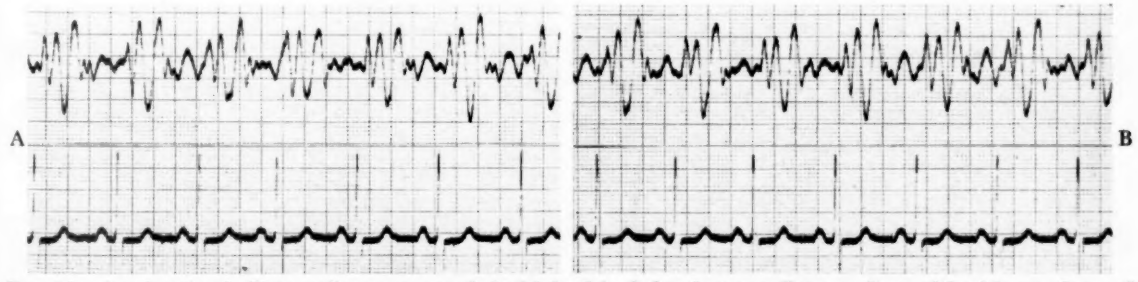

FIG. 16. Acceleration ballistocardiograms recorded with lead 1 of the electrocardiogram from girl with tetralogy of Fallot before (A) and after (B) 100-yard swimming race.

B). Normal grade and form patterns are present throughout. The large amplitudes at rest as well as the decline after the effort are relevant features to which further reference will be made elsewhere. But neither of these two findings is per se indicative of functional abnormality.

We found corresponding differences in amplitudes before and after exercise in several champion athletes. The whole issue deserves further study, and reference is made once more to the significance of the observation that the conspicuously high systolic amplitude in the BCG of champion track runners tends to be reduced greatly if a period of complete immobility precedes the recording of the tracing. In other words, a distinction must be made between pre-exercise ballistocardiograms taken in the basic state in terms of accepted experimental procedure in physiology, and pre-exercise records taken "at leisure."

Mechanisms of Cardiovascular Adjustment: The observation of suboptimal and abnormal ballistocardiograms in subjects capable of extraordinary physical performances is of profound importance from the point of view of the clinical physiology of the cardiovascular system. The case histories under review represent corresponding opposites to those mentioned above in which normal and optimal ballistocardiograms were found in persons afflicted with cardiac diseases—e.g., in the swimmer with tetralogy of Fallot; a similar functional state is presumed to have existed in the runner with aortic regurgitation and mitral stenosis; in the ski jumper in whose heart a bullet was embedded; and the long-distance runner with a large aortic aneurysm.

Evidently, there are two entirely different mechanisms of physiologic adjustment and compensation of the cardiovascular system to the impact of pathologic conditions. The one, present in the subjects referred to above, is characterized by effective adaptation within the heart itself, with the result that the energy yield during systole remains undisturbed by the mechanical or hemodynamic or structural abnormalities under discussion.

Quite a different mechanism of physiologic adjustment and compensation of the cardiovascular system to the impact of pathologic conditions must be postulated for the athletic subjects whose ballistocardiograms were of grade III or IV. We have seen several sportsmen belonging to this category, among them a 70-year-old tennis coach with a grade III BCG who played a daily average of eight sets. Here, the functional deficiencies of an inferior myocardium are effectively compensated by peripheral components of the circulatory system. Such a mechanism of compensation and, vice versa, of decompensation, was described by Eppinger[6] more than three decades ago.

Theoretical Considerations and Conclusions

Two theoretical formulations have emerged from these studies. One of these pertains to physiology, the other to pathology. Both are related to the question of the origin of the degenerative cardiovascular diseases. This point deserves emphasis, since few corresponding instances of physiologic components being associated in a direct or reverse cause-and-effect relationship with pathologic processes affecting blood circulation are known at present. Evidence has recently been adduced linking one such component, nutrition, with the pathogenesis of cardiac diseases. But this evidence has been deductive, resting in the main upon interpretation of statistical data.

The first of these two theories has been presented in a book,[9] which contains an account of the issue as a whole, including the presentation of clinical experiences with first-class athletes afflicted with heart disease. A brief reference to this issue was made in this paper. Apparently two cardiovascular determinators are involved in the integrative process through which physical performances of extraordinary magnitude are possible in cardiac patients. First, the degree of *stability of the underlying pathologic process*—e.g., in rheumatic and in coronary heart disease; and secondly, the scope of *extracardiac adaptation* to physiologic stresses such as exercise. It is of great interest that the concept of stability of the pathologic process affecting the myocardium has been evolved independently and through a very different methodologic approach by Beck.[11]

Another concept pertains to the contribution which cardiovascular studies of athletics, and more generally, of physical efficiency, have made to our knowledge of the *genesis of the degenerative cardiovascular diseases.* The facts on which this concept is based are essentially as follows:

(1) Well-trained and efficient subjects whose physical endurance is distinctly above that found among untrained young persons display cardiovascular characteristics of their own. These characteristics, reflected not only in ballistocardiographic records (Reindell,[4] Mel-

lerowicz[5]), are primarily physiologic in nature; functionally they are correlated to the exercise habits of the individuals concerned.

(2) Maintenance of the superior BCG which is found in well-trained subjects is dependent upon continuation of physical training. It is important to point out that, once they interrupt their training, even former Olympic champions no longer possess the cardiovascular features seen in the superbly fit track runners.

(3) Not every kind of exercise produces the cardiovascular adaptations under reference. The weight lifters as a group did not display the superior functional traits that were seen in the track men who participated in the NCAA Championships at Austin, Texas, in 1957.

(4) The presentation of suboptimal and abnormal ballistocardiograms from clinically healthy men who 20 or more years ago belonged to the champion class, and who must therefore be assumed to have then possessed hearts corresponding functionally to those from which the BCGs in Figure 4 were derived, focuses attention upon the nature of the stimulus requirements involved in the physiologic stress and response pattern under consideration.

(5) It has been demonstrated that within wide limits, form and grade defects of the ballistocardiogram of healthy and diseased persons are reversible through physical training. No other physiologic method of therapy is known to do likewise. It is therefore appropriate to point to the specificity of the procedure—physical training.

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Historical Milestones

Nineteenth-Century Descriptions of Atherosclerotic Occlusion of the Branches of the Aortic Arch

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Buenos Aires, Argentina

THE SYNDROME of brachiocephalic ischemia has received increasing and particular attention in the medical literature since 1950. It is variously named as "Takayasu syndrome," "brachial arteritis," "reversed coarctation," "aortic arch syndrome," "chronic subclavian-carotid obstruction," "Martorell-Fabré syndrome," "pulsus differens," "pulseless disease," and many more. Although the impalpability of the radial pulse as a clinical sign was already noted by William Harvey in a patient with a subclavian artery aneurysm,[1] most of the published papers ascribe to the Japanese ophthalmologist Takayasu the first original description of this condition. From an etiologic point of view it is convenient to distinguish those cases in which young females are principally affected, from the rest of the cases.[2] The first group seems to correspond to an inflammatory arterial disease of the giant cell type, which has a progressively downhill course and is usually refractory to medical treatment. The second group in the ischemic brachiocephalic syndrome comprises a variety of conditions, including syphilitic aortitis and atherosclerosis.

Amidst the French physicians of the second half of the nineteenth century, Henri Rendu and Michel Peter have presented observations of obliteration of the supra-aortic arterial trunks of atherosclerotic origin.

According to Ross and McKusick,[1] one of the first to report a case of aortic arch syndrome of atherosclerotic origin was Broadbent, in 1870. This patient, however, had a coincident syphilitic aortitis, which makes the pathologic interpretation difficult and inconclusive.

GUILLAUME DUPUYTREN

We have been fortunate to find the original reports of two cases of occlusion of the vessels arising from the aortic arch published in 1839 by Guillaume Dupuytren,[3] and a similar description of two cases by Rendu[5] and Peter[6] in 1890 and 1893, respectively. It is the purpose of this paper to present an English translation of these original observations and to briefly discuss their nature and significance, as well as some personal traits of their authors.

DUPUYTREN'S DESCRIPTIONS

Guillaume Dupuytren, in his *Leçons Orales de Clinique Chirurgicale*, published in 1839, described in "De la gangrene symptomatique par suite d'arterite," (pp. 273–274 and 279 of volume III, article VI), two observations of arterial occlusion of the subclavian and carotid arteries with resulting gangrene of the nose and fingers (Fig. 1). I have translated the observations from the original (Fig. 2) as follows:

CASE III. Symptomatic gangrene involving the nose and fingers. Death. Autopsy. Diseases of the heart and vessels.

A. G., a 69-year-old merchant, was admitted to the Hôtel Dieu March 21, 1825. He could not give any clue as to the origin of his malady. Only the following symptoms were found: the nose and the skin of the cheeks were of a black, cyanotic color. The right little finger was likewise of a black coloration in

its extremity. In all these regions the normal temperature and sensibility were extinguished. Prostration was extreme, the pulse intermittent. Respiration and speech were impaired (baths, infusion of melissa). On the 22nd the patient died in a state of marked agitation. At autopsy, necrotic lesions involving the skin of the nose, cheeks, the dorsal aspect of the right forearm, and the little finger and sacrum were present. The heart was enlarged, its right chambers contained yellow and black fibrinous clots. The left ventricular wall was markedly thickened. The mitral valve and chordae tendineae are ossified. The coronary arteries present ossifications. The origin of the aorta, as well as the transverse and thoracic portions, are diffusely involved with bony patches. The innominate, the right subclavian, and the common carotid arteries share the same alterations. Many regions showed a reddish color.

Like the previous observation we find gangrene coexisting with disorders of the heart and great arterial trunks. The site of the malady offers interest by itself, as in the great majority of cases the lower extremities are the affected (italics mine).

Case V. Symptomatic gangrene. Voluntary amputation of a finger. Progression of the disease. Phlegmon. Death. Autopsy.

M. Brochard, aged 63, noted pain in the lower limbs two years previously. These pains were later felt at the right hand, and particularly at the little finger, which became insensible. Blisters developed, filled with a serous content excessively fetid. Pain constantly increased and became so severe that Brochard, in an access of fury, himself severed with a knife the little finger, at the joint between the second and third phalanges. The process, instead of diminishing, made a rapid course, and September 9, 1828, Brochard was admitted to the Hôtel Dieu, ward Sainte Jeanne. The pulse was quick, the tongue covered with mucous, black at its base. The tumefaction gained the lower part of the arm. The fingers, wrist, and forearm were the site of excruciating pain. A diagnosis of symptomatic gangrene and diffuse phlegmon was made. The brachial artery was followed in a segment of its course and showed several points of ossification. On the 17th of September the state of the patient was not worse as far as gangrene was concerned. The phlegmon, on the contrary, had extended up to the superior part of the forearm. The mind was troubled, and on the 24th of September, death put to an end the sufferings of the patient.

At autopsy, the phlegmonous parts were bathed in pus, the muscles separated, and the little, ring, and middle fingers were necrotic. But the lesion that aroused attention was that of the vessels: The arteries of the axillae, arm, and forearm were inflamed at several points, and showed a great number of ossified plaques, which were also present in great number in the arteries of the lower limbs. The liver contained a cyst full of hydatids.

LEÇONS ORALES

DE

CLINIQUE CHIRURGICALE

FAITES A L'HOTEL-DIEU DE PARIS,

PAR

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Chirurgien en chef,

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Fig. 1. Title page from Dupuytren's book, volume III, second edition.[3]

COMMENT

Both patients reported by Dupuytren showed gangrene of the upper extremities, and in one of them necrotic lesions of the nose and cheeks were also present. It is unfortunate that no mention is made of symptomatology, except for the pain occurring in the terminal episodes. In this manner brachial or masseteric claudication, impaired vision, or syncope might have been noted.

Obs. III. — *Gangrène symptomatique attaquant le nez et les doigts. — Mort. — Autopsie. — Maladies du cœur et des artères.* — Gumery (Auguste), âgé de soixante-neuf ans, commerçant, entra à l'Hôtel-Dieu le 21 mars 1825. Lors de la visite, il ne put donner aucun renseignement sur l'époque de sa maladie ; on constata seulement les symptômes suivants : le nez était d'une couleur noire violacée; la peau des pommettes offrait la même teinte; le petit doigt de la main droite était aussi noir à son extrémité. Dans tous ces points la chaleur et la sensibilité étaient éteintes. L'affaissement était

Fig. 2. Reproduction of Dupuytren's first observation of atherosclerotic occlusion of the branches of the aortic arch.[3]

In the first patient "the pulse was intermittent, and respiration and speech impaired," suggesting heart disease, possibly left ventricular failure with atrial fibrillation. Aphasia due to an ischemic cerebral lesion could have been the mentioned difficulty of the speech. The pathologic examination confirmed the presence of heart disease of the arteriosclerotic type, involving the coronary arteries and mitral valves. The marked left ventricular hypertrophy could be explained on the basis of arterial hypertension. The branches of the aortic arch, except the left subclavian, were evidently the site of atherosclerotic occlusion. The reddish color present in some parts could correspond to recent thrombosis. Two shrewd remarks of Dupuytren's are worthy of mention—the "coexistence of gangrene with disorders of the heart and great vessels," and the observation of the interest of the case "as in the great majority of patients the lower extremities are the affected." He thus already had noted the rarity of arterial obstruction of the upper extremity.

In the second patient, the presence of intermittent claudication of the lower limb seems plausible. The suppurative process involving the right arm followed the autoamputation of the little finger, a fact which speaks by itself as to severity of the pain and the courage of the patient.

The pathologic findings were remarkably similar to those of the previous case, including the simultaneous occurrence of occlusive lesions in the lower limbs. In addition, aortic stenosis was present.

A point which merits discussion is the etiology of the process. The age of both patients, the involvement of the lower extremities as well as the coronary vessels by the vascular disease and the pathology description all point to atherosclerosis with secondary thrombosis and calcification. It is difficult to ascribe another origin to these lesions or to interpret their pathologic nature in a different way. Although the patchy calcified plaques of the aortic arch could be of syphilitic origin, this disease would not involve the arterial tree of the lower extremities. The presence of aortic stenosis is another argument against the syphilitic etiology, as it is currently accepted that this process rarely, if ever, causes stenotic valvular lesions.

The detailed necropsy report and the clinicopathologic correlation are remarkable for a surgeon of that time, if one considers that the majority of surgeons were brilliant and rapid operators but not particularly distinguished in clinical surgery or surgical pathology. In fact, Dupuytren can be considered as one of the founders of clinical surgery. The symptoms, however, were not carefully taken into account. Physical examination is adequate, although no mention of the arterial pulses is made. That Dupuytren looked after the arterial pulses, however, is evident after reading Case IV, which is a detailed description of aortoiliac thrombosis. Here it is stated that "the left femoral pulse was almost imperceptible." Further comment on this case, however, is beyond the scope of this paper.

BIOGRAPHICAL NOTES ON DUPUYTREN

The reading of Dupuytren's works makes apparent that he was not only a brilliant operator, but also a skilled clinician at the bedside. The physical examinations are carefully performed, and the clinical observations almost always followed by the autopsy record. He was fortunate enough to have Bichat and Corvisart as teachers, and undoubtedly as the first sparked the young Dupuytren with a deep interest in pathologic anatomy, the second inculcated him with the importance of a detailed physical examination.

Dupuytren was the greatest representative of mid-nineteenth-century French surgery. He was born on October 5, 1777, at Pierre Buffière, a town near Limoges, the son of a humble lawyer with limited means. It is said that his graceful face and blond hair captivated a rich woman from Toulouse, who tried to abduct him, but his father found him. Again, in 1789, when he was 12 years old, an officer of the French cavalry was astonished by the justness and vivacity of the answers from the child. The officer proposed to take the boy to Paris, this time with his father's consent. At his arrival at the capital, he was placed at La Marche college, directed by the officer's brother, M. Coësnon. His studies were brilliant, and the numerous prizes in philosophy indicated his early rightness of judgment.

At the age of seventeen he obtained the position of dissector, but his financial means were scanty at this time. An anecdote bespeaks his pride of character. Saint-Simon, desiring to have Dupuytren as an adept to his doctrines, and after an animated conversation, left two hundred francs in the shabby kitchen. When Dupuytren after a while perceived the money, he ran after Saint-Simon and said to him, "Sir,

you have forgotten your money." "That's true," was the only answer of the philosopher.

In 1801, being now 24, he obtained the post of chief of anatomical practice. From this moment on he cultivated with ardor the field of pathologic anatomy. With his friend, Professor Dupuy, he contributed papers containing original observations on physiology. From now on, his career was a series of uninterrupted and brilliant triumphs. In 1808, at the age of 31, he was appointed assistant chief surgeon to the Hôtel Dieu. Three years later we find him as professor of operative surgery, and surgeon-in-chief in 1815. After one year he was created a baron, and given the Order of St. Michael. In 1820 and 1821, he was named consulting surgeon to Louis XVIII and Charles X, respectively. He was also a member of the Academy of Sciences and of the Royal Academy of Medicine. He was now famous in the medical world of the continent and abroad. His name spread throughout Europe, and his surgical practice and income increased enormously. A great fortune was thus formed. The following anecdote speaks, however, of his generosity. When Charles X, living in exile after a revolution, was known to be in economic difficulties, Dupuytren sent him this message: "Sir, thanks in part to your favors, I possess three millions. I offer you one; I left the second to my daughter, and I keep the third to my old days."[4]

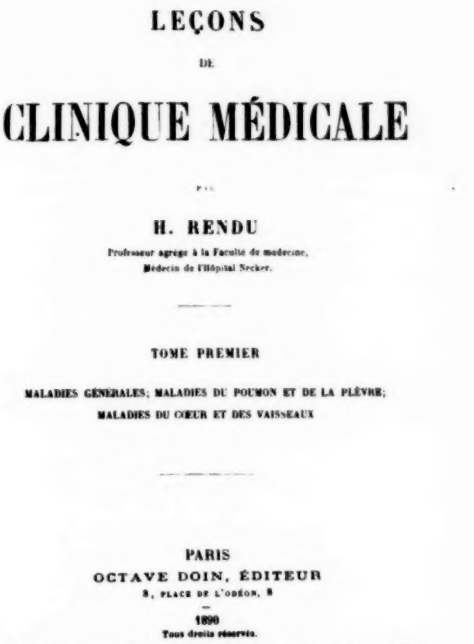
As a man, it seems that Dupuytren was not an agreeable or charming personality. It is said that he was rude and cynical, especially with his rivals. These traits of his character contributed to the growth of many of his enemies.

To his original descriptions of the permanent retraction of the fingers, lacrimal fistulae, arterial ligatures, strangulation of hernia, should be added, we believe, the atherosclerotic occlusion of the branches of the aortic arch.

Henri Rendu

Henri Rendu, in his *Leçons de Clinique Médicale*,[5] (volume I, pp. 416–417, 419, and 425) (Fig. 3), reported in detail the history of a 53-year-old male with dyspnea on effort, orthopnea, and retrosternal oppression. I have translated the paragraphs relevant to the present report:

. . . We have seen that the carotids beat unequally in the neck, but both seem normal: Their function is regular, as the patient does not complain of any functional cephalic trouble. The subclavian arteries are more dissimilar. The right is more elevated than


LEÇONS

DE

CLINIQUE MÉDICALE

PAR

H. RENDU

Professeur agrégé à la Faculté de médecine,
Médecin de l'Hôpital Necker.

TOME PREMIER

MALADIES GÉNÉRALES; MALADIES DU POUMON ET DE LA PLÈVRE;
MALADIES DU CŒUR ET DES VAISSEAUX

PARIS
OCTAVE DOIN, ÉDITEUR
8, PLACE DE L'ODÉON, 8

1890
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FIG. 3. Title page from Rendu's work, volume I.[5]

the left at the supraclavicular region, the pulse is likewise more forceful. It is therefore possible that at their origin they present a difference in caliber. But while examining the radial arteries, an unexpected phenomenon is found—the right radial pulse is excessively feeble, and can hardly be felt. The left radial is absent altogether; the arterial wave, if it arrives at all to the forearm, is so attenuated as to be no longer perceptible. If we try to establish the point where the artery is obstructed, we arrive at the conclusion that the stenosis is located between the subclavian and axillary. Over the clavicle, the pulse is forceful, beneath the clavicle, it is not present. This finding is so clear-cut that we ask ourselves how in these conditions, the arterial circulation of the upper extremity can be effectuated. Moreover, it is certain that no serious circulatory interference is present in this patient. He does not complain of numbness, formication, or paresis of the arm. No functional troubles are evident, and the fact would be completely overlooked unless an attentive search of the status of the arterial system is performed. A particular anatomic disposition explains this curious functional immunity. The acromiothoracic arteries in man have developed to a marked degree. Leaving the supraclavicular fossa, they obliquely passed in front of the clavicle, and from there descend to the deltoid-pectoral sulcus, following a sinus course. They form large anastomoses between the large muscular arteries of the arm and the subclavian system. This is an arterial anomaly, as the acromiothoracic trunk habitually leaves the axillary below the clavicle; but in its general distribution it follows the same course, and responds to the same physiologic purpose;

it is a derivation channel. Here, because of the obliteration of the axillary artery, it has developed enormously and its size is equal to that of the radial artery. It is probable that the other deep anastomotic arteries (circumflex and scapular) have similarly developed. It is in this way that the arterial circulation of the upper limbs can be maintained without limitations. It also explains the paradoxical fact, that while the right axillary cannot be palpated, the right radial pulse is perceptible; the circulation is re-established through anastomoses. . . .

. . . The arterial lesions are not limited to the upper extremities; they extend to the vessels of the lower limbs. The femorals are enormous, hard, and like cartilage. The tibials and dorsalis pedis form hard and flexuose cords. Atheroma is therefore generalized. The absence of the radial pulse is more difficult to interpret. I have shown in a recent report to the Society Hospitals (1887) the value of this sign as an index of latent aneurysm of the aortic arch, and I believe that the present case confirms the rule. *Ordinarily the disappearance of the radial pulse is due to the obliteration of the subclavian artery by the clots that cover the aneurysmal cavity. But this pathogenesis is not constant, and we know perfectly that an atheromatous plaque developed at the level of the insertion of the aortic branches begins to diminish its lumen, to end in a complete obstruction. I have had the occasion to verify two cases of this kind, where the radial pulse was absent during life, the anatomic explanation being an atheromatous degeneration localized at the origin of the subclavian artery. This is, as you know, a frequent lesion in the coronary arteries, and can also be localized at the point of emergence of the great vessels from the aortic arch* (italics mine).

Autopsy of this patient showed diffuse dilatation of the aortic arch. The insertion of the innominate artery is free from lesions. On the contrary, at the origin of the left subclavian artery exists a calcified atheromatous plaque that perceptibly diminishes the arterial caliber. During the first 4 cm of its course, however, it is dilated. At the point of insertion of the acromiothoracic artery the lumen suddenly diminishes to a fibrous cord. . . At the level of the insertion of the acromiothoracic artery, calcified atheromatous plaques can be seen, with the same appearance as those present at the origin of the left subclavian. The innominate artery is relatively little atheromatous, but beneath the insertion of the acromiothoracic lesions of the same kind as those on the left side can be seen, considerably diminishing the arterial caliber. . . The heart is enlarged; the left ventricle is dilated and hypertrophied. The muscular wall measures 3 cm. The mitral and aortic valves are normal. The coronary orifices are patent, and present only a few atheromatous plaques.

COMMENT

Of Rendu little is known, except by the attachment of his name together with Osler's, to

LEÇONS

DE

CLINIQUE MÉDICALE

PAR

MICHEL PETER

PROFESSEUR DE CLINIQUE MÉDICALE A LA FACULTÉ DE MÉDECINE DE PARIS
MÉDECIN DE L'HÔPITAL NECKER
MEMBRE DE L'ACADÉMIE DE MÉDECINE

Et quasi cursores vitai lampada tradunt
nostra

TOME TROISIÈME

PARIS
ASSELIN ET HOUZEAU
LIBRAIRES DE LA FACULTÉ DE MÉDECINE
PLACE DE L'ÉCOLE-DE-MÉDECINE

1893

FIG. 4. Title page from Peter's *Leçons de Clinique Médicale*, volume III.[6]

hereditary hemorrhagic telangiectasis, a condition which he described in 1896. He was a pupil of Potain, in whose mastership undoubtedly Rendu found much encouragement and inspiration. His *Leçons de Clinique Médicale* is dedicated to Potain in the following words: "My dear Maître: Placing under your auspices this humble work, I accomplish a proper duty of recognition, as following your wise lessons, I have understood everything that can be obtained from clinical observation, when it is guided by a keen spirit, and a sure judgment." Rendu also made interesting observations on chronic constrictive pericarditis, atherosclerosis, and abdominal aortic aneurysm.

The patient previously described presented an obliteration of the origin of the left subclavian artery, whose atherosclerotic nature is established by the author. To this lesion, a segmental occlusion of both axillary arteries must be added. The interpretation of the lack of symptoms, and of the collateral circulation, is remarkable. As in the two cases presented by Dupuytren, this case had arterial lesions in the lower limbs, an additional evidence of the atherosclerotic nature of the process. It is to be noted that Rendu states that he observed another two patients with absent radial pulse, autopsy showing an atheromatous lesion at the origin of the subclavian artery. It is unfortunate that Rendu

does not give additional clinical data on these two patients.

Michel Peter

The third description of aortic arch syndrome reported during the nineteenth century belongs to Michel Peter. A pupil of Trousseau, he was a prolific writer and contributed a book on cardiac disease. He was somewhat dogmatic in his views, and an ardent enemy of the bacterial theory of Pasteur. A rival of Potain, whom he repeatedly contradicted, he was obviously less distinguished in his accomplishments, either by nature or by study.

The case report presents a 47-year-old woman complaining of upper retrosternal pain. Examination of the heart revealed an aortic diastolic murmur.

> . . . In the first place, let us examine the peripheral arteries. The right radial pulse presents to the finger, as well as to the sphygmograph, the qualities of the Corrigan pulse. The left radial pulse does not present these characteristics; it is feeble and delayed. The right carotid and right subclavian arteries are bounding, these same vessels do not bound at the left side. There must exist at the origin of the left carotid and subclavian, atheromatous or calcareous plaques stenosing their orifices. (*Leçons de Clinique Médicale*,[6] pp. 624–625, volume III) (Fig. 4).

The lack of autopsy proof in this case does not permit establishing with certainty the true nature of the process. The coexistence of aortic insufficiency could indicate a syphilitic aortitis as the cause of the absent pulses. The age and sex of the patient, moreover, do not permit the exclusion of an inflammatory arterial disease, representing Takayasu syndrome. This case has been included, however, on the basis of the assumption of Peter. Be it right or wrong, it indicates his knowledge of atherosclerotic occlusion of the branches of the aortic arch as a clinical entity.

The observations herein reported can be considered examples of the traditional French clinical medicine and surgery, emphasizing history and physical examination as the basis for diagnosis, as well as the importance of postmortem findings and clinicopathologic correlation for an accurate knowledge of disease phenomena. Perhaps Achard has aptly defined it: "Science d'abord, art ensuite, jugement toujours."

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Case Report

Paroxysmal Auricular Flutter and Right Bundle Branch Block Following Digitalis Therapy*

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DIGITALIS and its preparations are very potent drugs. Since the time of Withering signs and symptoms of overdosage are very well known. Cardiac arrhythmias due to digitalis intoxication are better recognized today. Such arrhythmias may have serious implications and require proper diagnosis and treatment. For this reason digitalis should not be given indiscriminately without proper surveillance of the patient and without awareness of its dangers.

The purpose of this paper is to report a patient with rheumatic heart disease, who developed paroxysmal auricular flutter with 2:1 response and right bundle branch block associated with severe symptoms, and who responded well to treatment with procaine amide.

CASE REPORT

Th. A., a 55-year-old woman, entered the hospital on November 28, 1957, complaining of progressive shortness of breath, palpitation and fatigue of two months' duration. The patient had been told by the family doctor that she had rheumatic heart disease for several years. Since 1952 she complained of shortness of breath after exertion, increased fatigue, and palpitation. For this reason she was given digitalis, but because of her poor mental condition she was unable to confirm the duration and the daily dose of the treatment.

Physical Examination: The patient was a rather thin woman in acute distress. She appeared dyspneic, orthopneic, slightly cyanotic with distended jugular veins and ankle edema. She was afebrile and had irregular rhythm with a heart rate of about 110/min. The respiratory rate was 30/min. The blood pressure 120/60.

The heart was enlarged. A grade 4 systolic murmur was present at the apex and was transmitted to the axilla. A loud 1st sound with an opening snap and a diastolic rumble were also present at the apex. A soft diastolic murmur was present at the 3rd left intercostal space transmitted across the left sternal border. P_2 was loud. Moist rales in the posterior bases of both lungs were present. The liver was enlarged about three fingerbreadths below the right costal margin, and grade 2 pitting edema was present in both ankles.

The patient was diagnosed as having rheumatic heart disease with mitral stenosis and insufficiency, aortic insufficiency, and cardiac decompensation. Since the previous amount of digitalis was not known, she was redigitalized.

Laboratory Data: The red and white blood cell counts were normal; Hgb 13 g. Blood sugar 130 mg, blood urea 52 mg, sedimentation

* From the Division of Cardiology of the Hippokration University Hospital of Athens (Director, Professor G. Michaelides).

rate 36 mm in the first hour. Urinalysis showed specific gravity 1017, albumin 2 plus, sugar negative. An ECG revealed auricular fibrillation with a ventricular rate of about 110/min and left ventricular hypertrophy. A chest x-ray revealed a heart enlarged to the left and right.

Hospital Course: The patient received during the first 12 hours 0.25 mg of digitoxin intravenously and 0.2 mg by mouth. The next day she received another 0.25 mg intravenously and 0.1 mg by mouth. During the night the patient developed a tachycardia of 150/min. The potassium solution for intravenous use, we gave 10 cc of 1 per cent procaine amide (Pronestyl) intravenously under electrocardiographic guidance. During the last part of the injection the appearance of the complexes changed, and although the tachycardia persisted, the RBBB disappeared. We continued one gram of Pronestyl intramuscularly every four hours. The same night the heart rate slowed to 120/min. Lead V_1 of the ECG taken at this time is shown in Fig. 1B. The condition of the patient was much better.

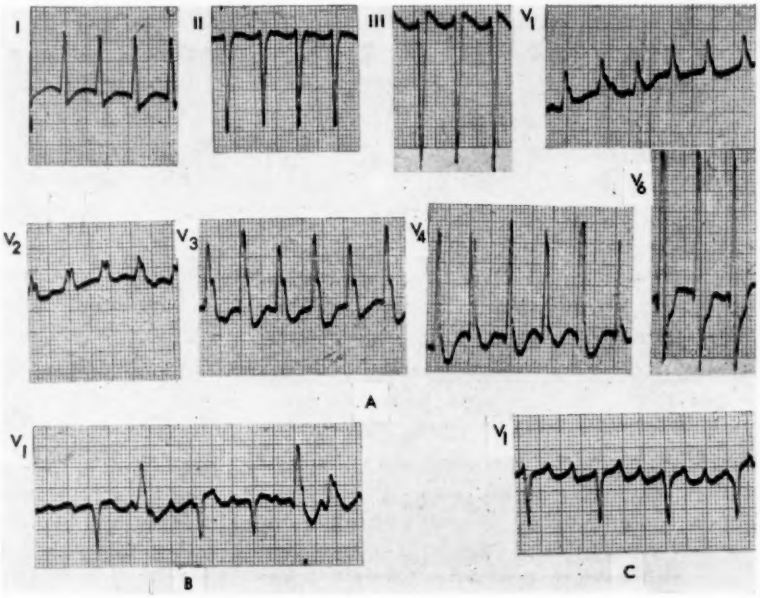

FIG. 1. (A) Tracing taken on Nov. 30th after a total dose of 1.3 mg of digitaline nativelle. It shows auricular flutter with 2:1 A-V response, right bundle branch block and electrical alternans. (B) Lead V_1 of the ECG taken after administration of 2 g of pronestyl. (C) Lead V_1 of ECG taken on Dec. 2nd. Pure auricular flutter is present, with a ventricular rate or about 90 per minute (3:1 A-V ratio).

intern thought that the patient needed more digitalis and without a new ECG administered another 0.5 mg of digitoxin intravenously. The patient passed a very difficult night and the next morning was transferred to the Cardiac Clinic of the Hospital in extremis. Here she appeared stuporous, perspiring, vomiting and had a pulse rate of 170/min. The situation was diagnosed immediately as digitalis intoxication.

An ECG was taken (Fig. 1A) and showed auricular flutter with 2:1 A-V response and right bundle branch block. Because of the lack of

On December 2, two days after the onset of the tachycardia, the heart rate was about 90/min and the ECG showed pure atrial flutter with 3:1 A-V response (Fig. 1C). Pronestyl was now given by mouth. The next day the pulse was down to 80/min, but she still showed pure flutter. She appeared markedly improved and the medicine was discontinued. That same evening she complained of weakness in moving her lower extremities. A neurologic examination revealed absence of the tendon reflexes in both extremities. A spine x-ray

proved displacement of the fourth lumbar vertebra. She was transferred to the Department of Neurology where her cardiac status remained satisfactory with a weekly injection of 2 cc Thiomerin. However, she developed complete paraplegia a few days later. On January 3, she again received digitalis and two weeks later left the hospital.

Discussion

There is no question that the digitoxin (digitaline nativelle) administered to this patient was responsible for the ensuing severe arrhythmia. It is particularly noteworthy that the dose was not excessive according to the common practice of digitalization. It is true that in our case the previously received dose of digitalis was unknown. But taking into consideration that the doses given by the country doctors in Greece are usually very small, not exceeding 4 to 5 drops daily of digitaline, and that the patient was in heart failure upon admission, we felt that the patient was underdigitalized. It is known that occasionally auricular fibrillation and flutter may result from an excessive dose of digitalis because of the vagal effect of the drug which shortens the refractory period. On the other hand, the direct effect of digitalis on the auricular muscle tends to increase the refractory period. Between the vagal and direct auricular effect usually the vagal predominates and causes a decrease of the refractory period of the auricle.[1–3,10]

The second interesting feature of our case is the aberrant conduction due to delay in the right bundle branch. This could be the result of the toxic effect of the drug on the conductive system or a functional phenomenon of a fatigued myocardium during excessive tachycardia. It has been emphasized[4] that such aberration associated with auricular flutter may simulate ventricular tachycardia. The recognition of this deviation is of considerable importance in treatment and prognosis. The response to carotid sinus pressure is of extreme value in determining the type of the tachycardia.

Another interesting feature in the ECG is the presence of electrical alternans which is more pronounced in the precordial leads (Fig. 1A). This phenomenon may be present in many tachycardias due to digitalis intoxication.[9]

We have diagnosed this tachycardia as an auricular flutter with 2:1 A-V response. Another possibility, although not strong, is that this is a paroxysmal auricular tachycardia with block which sometimes follows digitalis intoxication as Lown and Levine have shown.[6,7] We believe that the ECG of our case does not fit this type of arrhythmia.

As stated earlier, digitalis may produce every known type of arrhythmia.[11,12] Development of any of the clinical or electrocardiographic evidences of digitalis poisoning demands immediate withdrawal of the drug. In addition, certain positive measures may be employed to regulate the rhythm, before irreversible damage is produced. The potassium salts given orally or intravenously are of extreme value in such cases.[5] Procaine amide is also very effective in the treatment of these arrhythmias.[13,14] Intravenous administration should be reserved only for critically ill patients who cannot take oral medication. In our case Pronestyl was given intravenously because of the critical condition of the patient, and it proved very useful with a dramatic response. This proves once more that Pronestyl is effective in treating patients with supraventricular arrhythmias.

Of further interest in this case is the fact that the toxic cardiac phenomena appeared earlier than the usual manifestations of toxicity. Such observations have been reported previously[8] and are of extreme importance when digitoxin is used.

We could final no causal relation between the paraplegia due to the displacement of the vertebra and the digitalis intoxication.

Summary

Paroxysmal auricular flutter with 2:1 response, right bundle branch block and electrical alternans were observed in a 55-year-old patient with rheumatic heart disease who received 1.3 mg of digitaline nativelle in 40 hours. Severe toxic phenomena of alarming and near fatal nature appeared later than the intoxicating action on the heart muscle and the conducting system. The patient responded very well to treatment with Pronestyl.

Considerable caution should be exercised in the administration of digitoxin preparations.

This case once more draws attention to the need of close supervision of patients receiving digitalis.

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Diagnostic Shelf

Reciprocal Beats Masquerading as Ventricular Captures*

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THE ACCOMPANYING ELECTROCARDIOGRAMS illustrate how a relatively minor and easily overlooked finding can furnish a necessary clue to appropriate electrocardiographic diagnosis.

The tracing in Figure 1,† taken from a 24-year-old woman four months after a Blalock-Taussig procedure, apparently represents a classical example of A-V dissociation (interference-dissociation), the final beat in the strip being the only normally conducted sinus beat. Except for three early beats (A, B, C), the ventricular rhythm is regular at a rate of 75. The atrial rate is somewhat slower so that the P waves constantly change their relationship to the QRS complexes. On three occasions P waves, appearing shortly after the QRS complexes, are followed by early ventricular beats showing aberrant conduction. These beats apparently represent typical "ventricular captures."

This record does not appear to be of any particular interest since the diagnosis of A-V dissociation with capture beats seems clear-cut. A minor finding, however, and the evaluation of its underlying physiology, enables one to modify the diagnosis and arrive at an alternative interpretation of the apparent captures.

Re-entry with Reciprocal Beats vs. Ventricular Capture: The sinus P waves in Figure 1 are all well pronounced, with an amplitude of 1.5 to 2 mm. The P wave that precedes the third "ventricular capture" (C), however, is small and indeed almost isoelectric. Such a P wave indicates the likelihood of an atrial fusion beat resulting from the simultaneous activation of the atria by a sinus and a retrograde impulse. If this is the case, at least part of the atria must have been activated by the retrograde impulse (partial atrial capture), and it is therefore clear that the

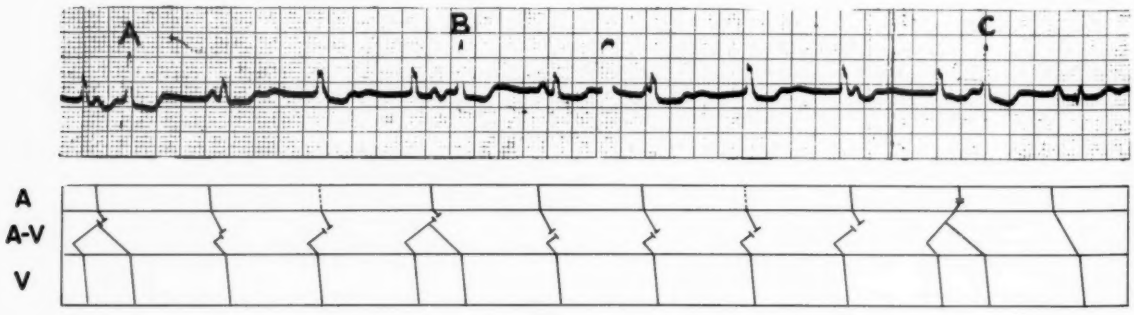

FIGURE 1

* From the Johns Hopkins Hospital and University Hospital, Baltimore.
† From the files of the Cardiac Clinic of the Harriet Lane Home, the Johns Hopkins Hospital.

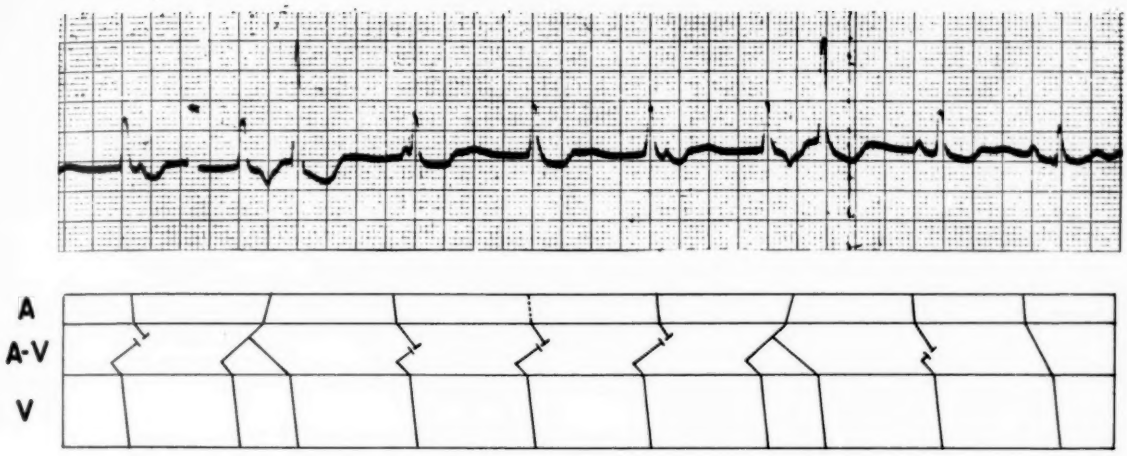

FIGURE 2

antegrade sinus impulse could not proceed to activate and "capture" the ventricles. If, then, this is not a *capture* beat, one is led to the conclusion that the retrograde impulse, before entering the atria, finds a return path to the ventricles and produces a *reciprocal* beat. It is striking that the coupling time of this reciprocal beat (0.37 second) is identical with the coupling times of the first and second early beats (A, B), and this in turn favors the assumption of the same re-entry mechanism in all three early beats. In these three beats, the retrograde A-V impulse apparently reaches the level of the re-entry pathway before interfering with the descending sinus impulse. In the first two beats the interference takes place within the A-V tissues; in the third beat, in the atrial muscle. These relationships are graphically represented in the diagrams below the tracing.

As the diagram illustrates, some retrograde conduction of the A-V impulse occurs with every beat. In the regular beats this interference of retrograde and antegrade impulses takes place below the level of the re-entry path, so that the retrograde conduction remains invisible or latent. When interference occurs above the re-entry pathway, but still within the A-V tissues, the resulting reciprocal beats masquerade as capture beats. Only when interference occurs within the atrial musculature is the clue for proper diagnosis afforded.

The correctness of this diagnosis is substantiated by a later tracing from the same patient (Fig. 2), showing definite reciprocal rhythm with clear evidence of retrograde conduction to the atria (complete atrial capture) and with a coupling time identical with that of the reciprocal beats in Figure 1.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Mitral Stenosis and Gallstones

RECENTLY Drs. Frank Glenn and S. Frank Redo (Department of Surgery, New York Hospital) reviewed the records of 300 patients operated upon for mitral valvular heart disease. This study revealed that 43 had gallbladder disease, an incidence of 14.3 per cent. The incidence in the general population is estimated at 10 per cent. Diagnosis was established at surgery or postmortem in 32, and by oral cholecystography or intravenous cholangiography in 11 cases. Oral cholecystography properly done provides information that has been shown to be dependable in establishing disease of the gallbladder in over 95 per cent of cases. In all patients with mitral stenosis—particularly women, who constitute the greatest proportion of all reported series of mitral stenosis—a gallbladder series is indicated whether or not a history suggestive of biliary tract disease is obtainable.

Acute cholecystitis following operations unrelated to the biliary tract is not uncommon. In the majority of instances when this occurs as a postoperative complication, it develops in a gallbladder containing stones. There have been several instances of acute cholecystitis following mitral valvulotomy.

Immediately after valvulotomy, a patient with mild right heart failure may have congestion of the liver with some enlargement and tenderness particularly over the gallbladder region. A differential diagnosis between right-sided heart failure and acute cholecystitis may be difficult. A previous examination of the biliary tract is of great help in the evaluation of such a patient.

In patients with mitral valvular heart disease who develop acute cholecystitis following valvulotomy, symptoms and findings often tend to persist and even progress so that operation is mandatory. This additional burden superimposed upon cardiac patients before they have recovered from the discomfort and pain of a thoracotomy is undesirable. This had led the authors to formulate the policy that provides for (1) an evaluation of the biliary tract for all patients being considered for mitral valvulotomy and (2) unless the indications for the surgical correction of the mitral stenosis are most urgent, biliary tract disease, if present, is treated first. Usually cholecystectomy is done alone, or is combined with common duct exploration. This has been well tolerated by patients with moderately severe mitral stenosis. Three weeks or more thereafter, the mitral stenosis is corrected.

Direct Left Ventricular Puncture

One of the newer methods of studying cardiac dynamics is percutaneous left ventricular puncture. A recent paper describing the use of this technique in the evaluation of aortic and mitral stenosis was presented recently by Dr. Paul N. Yu and associates of the University of Rochester School of Medicine (*Am. Heart J.* 55 : 926, 1958).

Percutaneous left ventricular puncture, performed according to a method modified from that of Brock and associates (*Thorax* 11 : 163, 1956), was combined with right heart catheterization in a study of 10 patients with aortic stenosis, 5 with both mitral and aortic stenosis, 8 with mitral stenosis, and 7 with other cardiovascular diseases.

In this technique, a 19-gauge needle connected to a three-way stopcock and a syringe of heparinized saline is inserted through a locally anesthetized site on the anterior chest wall, 1 cm below and lateral to the cardiac apical impulse. The needle is advanced along a line drawn between the second right costochondral junction

and the apical impulse, with a posterior inclination of 45 degrees. When the mass and movement of the left ventricle is felt, the needle is advanced more rapidly until blood appears in the aspirating syringe. An anesthetist and a thoracic surgeon are in attendance during the procedure, and the electrocardiogram is monitored continuously. The duration of the puncture itself is usually not longer than five minutes. No serious complications were observed following the procedure.

Comparison of heart rate, systemic arterial pressures, and arteriovenous oxygen difference before and during left ventricular puncture supported the statement of Brock and associates (cited by Yu *et al.*) that the puncture itself does not alter hemodynamics enough to affect the reliability of the information obtained.

The simultaneous measurement of pressure gradients and blood flow across both the aortic and mitral valves made possible by this technique yields valuable information regarding the severity of stenosis of each valve.

Patients with a calculated aortic valve area of 0.5 sq cm or greater were found usually to have a normal or slightly reduced aortic blood flow and a normal or slightly increased left ventricular diastolic pressure. Total left ventricular work was moderately or markedly increased. In contrast, patients with aortic valve areas of 0.5 sq cm or less had reduced aortic blood flow and elevation of left ventricular diastolic pressure. Total left ventricular work was normal or slightly decreased.

In addition to defining the diastolic pressure gradient across the mitral valve, measurement of left ventricular diastolic pressure was found useful in detecting the presence of left ventricular decompensation in a small group of patients with mitral stenosis and myocardial insufficiency. This has clinical significance in the selection of patients for mitral valve surgery.

Readings in Cardiology

From time to time, interesting books which ordinarily might escape the attention of cardiologists will be briefly reviewed in these columns.

Virus and Bacterial Myocarditis. Recent advances in the discovery of new viruses and in the recognition of human virus diseases have been remarkable. These discoveries are important because myocarditis has been described not only as a result of poliomyelitis infection, but due to infection with influenza, psittacosis, primary atypical pneumonia, Coxsackie B viruses, adenoviruses, and the viruses associated with infectious mononucleosis, epidemic hemorrhagic fever and mumps.

In addition, bacterial myocarditis can occur during the course of lobar and bronchopneumonia, diphtheria, scarlet fever, meningitis, typhoid, brucellosis, tularemia, acute nasopharyngitis, tuberculosis, staphylococcal and streptococcal septicemias, and as a result of rickettsial, spirochetal, fungal, and other parasitic infections.

Recent reviews by Silber (*Ann. Int. Med.* 48: 228, 1958) and Manion (*A.M.A. Arch. Path.* 61: 329, 1956) present the clinical picture of virus and bacterial myocarditis. A full discussion is available in two interesting basic bacteriology and virology books that have just been published, *Viral and Rickettsial Infections of Man** and *Bacterial and Mycotic Infections of Man.*†

These books are complete, authoritative and easy to read. They admirably bridge the gap between the ordinary textbook of bacteriology and the standard textbook of medicine, and should be very valuable to the cardiologist who is interested in myocarditis. E. G.

**Viral and Rickettsial Infections of Man*, ed. 3, edited by Thomas M. Rivers and Frank L. Horsfall, Jr. J. B. Lippincott Company, Philadelphia, 1958.

†*Bacterial and Mycotic Infections of Man*, edited by Rene J. Dubos. J. B. Lippincott Company, Philadelphia, 1958.

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, the JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Mitral Surgery in a Young Girl

Query: A 12-year-old girl has developed mitral stenosis following acute rheumatic fever two years ago. Her exercise tolerance is moderately impaired by dyspnea and fatigue. Should mitral commissurotomy be performed at the present time? What are the chances of restenosis?

Answer: In a personal experience with over 1500 cases of rheumatic heart disease with mitral valve involvement the indication for surgical relief of stenosis has been present in less than a dozen instances under the age of 18 years. Indeed, the advisability of surgery in a few of these after surgical exploration seemed questionable.

In the case of the girl under consideration, the short interval between the attack of rheumatic fever and the development of symptoms suggests that the dyspnea and fatigue may not all be related to the valve lesion. Auscultatory evidence of mitral valve disease is not unusual two years after acute rheumatism, but the production of tight stenosis in this short time seems unlikely. Definite evidence of serious mitral obstruction on clinical grounds supported by catheterization studies is required before surgery is considered.

If the presence of tight mitral stenosis is confirmed, and there is significant limitation of exercise tolerance, then surgery should be considered on the same grounds as in an older patient. Active adolescents may be more liable to acute pulmonary edema than the placid older person.

The possible complications of commissurotomy are the reactivation of rheumatic fever and the development of restenosis in later years. If there is evidence of an active rheumatic state at present, surgery should of course be postponed, unless needed to save life. If there has been no recognizable rheumatic activity for two years, the risks of reactivation are probably not great. Many postoperative changes attributed to rheumatic recurrence in the past were probably nonrheumatic pericardial reactions. The possibility of further stenosis following surgery at this age cannot be excluded. At present we have no information on this except to state that in my personal experience none of the patients under 18 years old so treated have developed restenosis as yet. If commissurotomy is needed to restore the child to health I would not withhold it. If further surgery is needed later, our experience indicates this would not present too great difficulty.

ROBERT P. GLOVER, M.D.
Philadelphia, Pa.

Letter to the Editor

In a Letter to the Editor in the March, 1959, issue Dr. Jacob Alperin draws particular attention to the hardened coconut oil component of Emdee Margarine and includes the observation, "It seems pointless to advise a patient to use skim milk instead of whole milk and yet allow him Emdee Margarine which contains 17 per cent coconut oil." Aside from the fact that the figure we reported for coconut oil was 15 per cent, instead of 17 per cent, we cannot help but disagree with Dr. Alperin's conclusions.

The literature is replete with evidence showing that it is possible to prescribe cholesterol-decreasing diets in which saturated fats are not rigorously restricted, provided adequate amounts of unsaturated fats are included. Malmros and Wigand (*Lancet* 2: 1, 1957) demonstrated that the cholesterol-raising effect of coconut oil could be halted and even reversed by the inclusion of one-third parts of corn oil, and more recently Hashim *et al.* (*Am. J. Clin. Nutrition* 7:30, 1959) found that the combination of equal parts of coconut oil and safflower oil produced the same reduction in cholesterol levels as safflower oil alone.

When Emdee Margarine is used to replace other solid fats in the diet, so far as practical, Terman (*Geriatrics* 14: 111, 1959) showed that it is, indeed, wholly unnecessary to advise the patient to use skim milk instead of whole milk in order to produce a cholesterol-lowering response. The particularly valuable feature of Emdee lies in the fact that it does not require a patient to alter his basic dietary pattern in order to achieve a significant reduction in cholesterol levels.

JAMES T. LOWE, PH.D.
Pitman-Moore Company
Indianapolis, Ind.

Book Reviews

Atlas d' Electrocardiographie, by V. Fattorusso and O. Ritter. 5 eme édition, Masson et Cie, Paris, 1958, pp. 311, fr. 3600.

The success of this book is due to its ingenious presentation—i.e., concise clear text, orderly, well arranged, and synchronized in relation to the illustrations and their legends.

This fifth French edition has new chapters dealing with vectorcardiography and certain arrhythmias.

This atlas has become a small treatise in which no aspect of electrocardiography is disregarded. It enables the student and the internist as well as the cardiologist to find the chapters of interest rapidly and read the essentials of each subject. Its chief advantage is its practicability for all. R. Heim de Balsac, M.D.

Electrocardiography, by Michael Bernreiter. J. B. Lippincott Company, Philadelphia, 1958, pp. 133, $5.00.

This text is a very abbreviated presentation of the subject of electrocardiography. Much of the explanation and discussion necessary for a clear understanding of the subject is lacking. Thus, the Einthoven triangle and the triaxial system are discussed without showing how the electrical axis is actually derived from the electrocardiogram. There is also no mention made of the significance of the electrical axis. Although the author speaks of the angle produced by the QRS and T vectors, he does not describe the ventricular gradient. For some reason, a few electrocardiograms presented as illustrations have the usual standardization in the conventional and unipolar extremity leads and half the standardization in the precordial leads. Figure 20 is supposed to illustrate a normal electrocardiogram but the T waves in leads V_1, V_2, V_3 being negative and in lead V_4 being isoelectric could certainly not be considered normal. He does not mention where such findings are occasionally observed in normal hearts.

The copy of the text sent to this reviewer has pages 122, 123, 126, 127, 130 and 131 all blank and page 128 is not numbered. The errors may not be present in all the copies. Some of the illustrations are well done and the book may be of some value as a brief review of the subject.

Louis H. Sigler, M.D.

Received for Review

All books received will be acknowledged in this column. Insofar as possible, as space permits, books of special interest will receive more extensive reviews.

Peripheral Vascular Diseases: An Objective Approach, by Travis Winsor. Thomas, Springfield, Ill., 1959, pp. 845, $16.50.

Physiology of Cardiac Surgery: Hypothermia, Extracorporeal Circulation and Extracorporeal Cooling, by Frank Gollan. Thomas, Springfield, Ill., 1959, pp. 96, $4.50.

Hypertension: The First Hahnemann Symposium on Hypertensive Disease, edited by John H. Moyer. Saunders, Philadelphia, 1959, pp. 790, $14.00.

A Textbook of Medicine, tenth edition, edited by Russell L. Cecil and Robert F. Loeb. Saunders, Philadelphia, 1959, pp. 1665, $16.50.

A Primer on Common Functional Disorders, by Jack W. Fleming. Little, Brown, Boston, 1959, pp. 174, $5.00.

Coronary Heart Disease, by John W. Gofman. Thomas, Springfield, Ill., 1959, pp. 353, $8.00.

Hypertensive Disease: Diagnosis and Treatment, by Sibley W. Hoobler. Hoeber, New York, 1959, pp. 353, $7.50.

That the Patient Moy Know, by Harry F. Dowling and Tom Jones. Saunders, Philadelphia, 1959, pp. 139, $7.50.

Anatomy and Physiology: Volume I, by Edwin B. Steen and Ashley Montagu. Barnes and Noble, New York, 1959, pp. 332, $2.50.

Angiocardiopneumographie Élargie: Méthode d'Opicification Vasculaire Générale par Voie Veneuse, by P. Viallet *et al.* Masson et Cie, Paris, 1959, pp. 110, 4400 fr.

Nursing Home Management, by Ralph C. Williams *et al.* F. W. Dodge Corporation, New York, 1959, pp. 230, $8.50.

Textbook of Pediatrics, by Waldo E. Nelson. Saunders, Philadelphia, 1959, pp. 1462, $16.50.

Announcements

Symposium on The Catecholamines in Cardiovascular Pathology

A symposium on "The Catecholamines in Cardiovascular Pathology" will be held at the University of Vermont, Burlington, Vermont, August 23–26, 1959, under the chairmanship of Wilhelm Raab, M.D., Professor of Experimental Medicine.

The preliminary program is as given below. Further information may be obtained by writing to the Chairman.

PRELIMINARY PROGRAM

AXELROD, J. (National Institute of Mental Health, Bethesda): The Metabolism and Physiological Disposition of Adrenalin.

BING, R. J. (Washington University Veterans' Administration Hospital, St. Louis): The Role of Catecholamines in the Etiology of Acute Heart Failure.

BOHR, D. F. (Physiological Laboratory, University of Michigan, Ann Arbor, Mich.): Analysis of the Mechanism of Action of Catecholamines in Vascular Smooth Muscle.

CHAPPEL, C. J. (Ayerst, McKenna and Harrison Limited, Montreal): Isoproterenol-Induced Cardionecrosis (jointly with DR. G. RONA).

DURY, A. (Dorn Laboratory for Medical Research, Bradford Hospital, Bradford, Pa.): Epinephrine Effect upon the Incorporation of Acetate-1-C^{14} into Aortal Lipids of Rabbit (jointly with DR. WERTHESSEN).

HOLLANDER, W. (Massachusetts Memorial Hospitals, Boston): Amine Oxidase Inhibitors and Angina Pectoris.

LEPESCHKIN, E. (DeGoesbriand Memorial Hospital, Burlington, Vt.): Epinephrine-Induced Electrocardiographic Changes.

MALING, H. (Laboratory of Chemical Pharmacology, National Heart Institute, Bethesda): Influence of Catecholamines upon Myocardial Fat Deposition and upon Serum Transaminase.

MELVILLE, K. I. (Department of Pharmacology, McGill University, Montreal): Coronary Flow and Heart Action Responses Following Depletion of Catecholamines by Reserpine.

MOYER, J. H. (Hahnemann Medical College and Hospital, Department of Medicine, Philadelphia): Effect of Various Catecholamines on Specific Hemodynamics When Given to Hypotensive, Normotensive and Hypertensive Subjects (jointly with DR. L. C. MILLS).

NAHAS, G. G. (Departments of Physiology, Pathology and Pharmacology, University of Minnesota Medical School, Minneapolis): Effects of Acute Arterial Blood pH Changes on Catecholamine Plasma Levels and Circulatory Adaptations (jointly with DR. B. MEHLMAN).

PEKKARINEN, A. (Pharmacological Institute, University of Turku, Turku, Finland): (a) The Adrenalcortical and Sympathetic Function in Heart Insufficiency; (b) Effect of Iproniazid, Reserpine and Ganglionic Blocking Substances on the Noradrenalin Content of Tissues.

PLUMMER, A. J. (Macrobiological Division, CIBA Pharmaceuticals Inc., Summit, N. J.); The Influence of Antihypertensive Agents upon Vascular Reactivity to Catecholamines (jointly with DR. F. F. YONKMAN).

RAAB, W. (University of Vermont, College of Medicine, Division of Experimental Medicine, Burlington, Vt.): (a) The Scope of Potential Pathogenic Effects of the Catecholamines; (b) Cholinergic-Adrenergic Disequilibrium Due to Lack of Physical Exercise.

REDISCH, W. (Goldwater Memorial Hospital, New York City): (a) Effect of Catecholamine Inhibitors on Peripheral Blood Flow; (b) Some Aspects of Interaction of Pressor and Depressor Agents in Normotensive and Hypertensive Subjects (jointly with DRS. K. DE CRINIS and J. N. STEELE).

RICHARDSON, J. A. (Department of Pharmacology, Medical College of South Carolina, Charleston): Circulating Epinephrine and Norepinephrine in Coronary Occlusion and Angina Pectoris.

SCHAEFER, H. (Department of Physiology, University of Heidelberg, Heidelberg, Germany): Subject to be announced.

SZAKACZ, J. E. (United States Naval Medical School, National Naval Medical Center, Bethesda): Quantitative Aspects of Norepinephrine-Induced Pathological Changes (jointly with DR. B. MEHLMAN).

WOODS, W. F. (Department of Pharmacology, Medical College of South Carolina, Charleston): Influence of Reserpine on Adrenal Medullary Responses to Direct Chemical Stimulation.

Seminar on the Electrocardiographic Exercise Test

A seminar on the electrocardiographic exercise test will be held at the DeGoesbriand Memorial Hospital, a teaching hospital of the University of Vermont College of Medicine, Burlington, Vermont, on September 19 and 20, 1959.

There will be a $10.00 registration fee for nonresidents of Vermont. Inquiries should be directed to Eugene Lepeschkin, M.D., Associate Professor of Experimental Medicine, University of Vermont College of Medicine, Burlington, Vt.